INDEX.

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Supplementum CLIII. *C. E. Nylund* (Helsingfors): Über die Untersuchungstechnik bei der Bestimmung von Nachtblindheit als Symptom von Vitamin-A-Mangel und Untersuchungen über das Vorkommen von Nachtblindheit und über ihre Abhängigkeit von der Vitamin-A-Zufuhr.

Pressor activity in blood and plasma from normal subjects and patients with essential hypertension.

By

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In spite of many attempts to demonstrate the presence of pressor substances in the blood of hypertensive patients the evidence still seems rather conflicting. Even with regard to the activity of normal blood or extract thereof the results differ.

Direct injection of moderate amounts of normal blood or plasma does not seem to produce any pressor effects as stated by a number of authors. Using extracts of normal blood or plasma some authors have observed pressor actions which, however, seem to have been somewhat irregular in their appearance and difficult to assay. Thus Page (1935) has reported the appearance of a pressor action in extracts of blood plasma which had been deproteinized with alcohol. The active substance was found to be soluble in water, alcohol, acetone and chloroform, but was not of lipoid nature. It was fairly unstable to heat. Ultrafiltrate from plasma did not contain the pressor substance. de Wesselow and Griffiths (1934) found with alcoholic extracts from various kinds of blood, including normal, a slight rise in blood pressure preceded by a fall, using urethanized cats as test animals. Other authors have failed to observe any pressor action with extracts from normal blood,

1 — *Acta med. scandinav.* Vol. CXIX.

either from human subjects or various animals. Enger and Jeling-
hoff (1941) made alcoholic extracts from blood plasma and serum
and stated that pressor activity was present in most extracts ex-
cept when heparine plasma in paraffinated vessels was used.

With extracts of blood from hypertensive patients, on the other
hand, several authors claim to have obtained pressor responses
on various test objects whereas others have been unable to find
any significant difference in comparison with blood extracts from
normotensive subjects. Positive results with blood from patients
with pale hypertension have been reported by Bohn and his asso-
ciates (1931, 1935) Heinsen and Wolf (1935), Govaerts and Dicker
(1936) and others. Bohn (1931) stated that alcoholic extracts of
blood from patients with normal blood pressure or »red» hyper-
tension gave a depressor effect only on the cat under urethane,
but that patients with »pale» hypertension (acute nephritis serving
as the typical condition) all gave pressor action without preceding
lowering of the blood pressure. Bohn and Schlapp (1935) were not
able to concentrate the pressor substance and like Page found con-
siderable difficulties in assaying the pressor effect. By using
plasma instead of blood they found that the depressor effect was
reduced.

Heinsen and Wolf (1935) reported the presence of tyramine in
blood from patients with pale hypertension but missed this sub-
stance in essential hypertension. Govaerts and Dicker interpreted
their pressor effects with hypertensive serum in a similar way. The
investigations of Enger and Arnold (1937) showed, however, that
the amount of tyramine is rather small in blood from hyperten-
sives, and probably cannot be responsible for the hypertension.
In later experiments Enger and Jelinghoff (1941) found a pressor
action in extracts from heparine plasma of human hypertensive
subjects with malignant sclerosis which they refer to nephrine, a
pressor substance previously demonstrated in extracts of kidney
by Enger (1939).

Negative results have been reported in a careful study by
Aitken and Wilson (1935) who tested alcoholic extracts and ultra-
filtrate of blood from patients with malignant hypertension. Capps,
Ferris, Taylor and Weiss (1935) found no pressor activity in ex-
tracts from normal and hypertensive blood. Page (1935) obtained
no evidence for an increase in pressor action from extracts of hyper-

tensive blood as compared with normal. Using extracts of heparine plasma from hypertensive dogs he sometimes found an even smaller effect than with plasma from normal dogs. In later experiments he found that when plasma from hypertensive dogs or patients (essential and malignant hypertension) was added to blood from a nephrectomised animal and perfused through a rabbit's ear, vasoconstrictor properties could be demonstrated, which were ascribed to angiotonin (Page, 1940). In an attempt to demonstrate pressor substances of renin type in blood from hypertensives negative results have been reported by Prinzmetal, Friedman and Oppenheimer (1938).

Heymans and Bouckaert (1938) found no increase in the vasoconstrictor properties in blood from dogs with chronic experimental hypertension, caused by renal ischaemia, whereas this was the case in animals rendered hypertensive by cutting the moderator nerves. de Wesselow and Griffiths (1934) found no striking difference between the action of alcoholic extracts from normal and hypertensive blood, though the effect was slightly greater with blood from essential hypertension. In some cases the extract of the whole blood gave a good response whereas plasma extract showed no action.

From this brief review of the literature it seems to follow that a certain pressor action may be obtained with extracts of blood from normal and hypertensive subjects though the effect is not constantly found. Any successful attempts to concentrate the active principle — if indeed the observed actions are due to a specific substance — have not been reported, as far as we have been able to find. The results diverge with regard to the alleged increased presence of pressor substance in the blood in hypertension. The bulk of evidence rather speaks against the presence of greater amounts of pressor substances in hypertensive blood as compared with normal blood, at least in the important group classified as essential hypertension.

In the light of recent research on the mechanism of hypertension due to renal ischaemia we have made some experiments in order to test the question anew as to the presence of pressor activity in blood from hypertensives. The material used has consisted of normal subjects and hypertensives, mostly cases of essential hypertension.

Methods.

The samples of normal blood were obtained chiefly from medical students about 20 years old, male and female, and the hypertensive blood from patients in the Royal Serafimer Hospital and the Karolinska Sjukhuset.[1] In total 74 samples of hypertensive blood and 24 normal bloods were tested. In addition pooled samples from groups of normals and hypertensives were tested in several cases.

The blood was drawn from the cubital vein and treated according to the varying procedures described below.

a. The blood — 100—400 ml — was allowed to flow directly in a vessel containing 3 times the blood volume of boiling hot alcohol. The mixture was left in the refrigerator for a few hours, filtered and evaporated in vacuo at low temperature to a few ml volume. 10 volumes of methyl alcohol were added, the precipitate filtered off, the clear solution evaporated to nearly dryness and taken up in a few ml water. This solution was then neutralized with H_2SO_4 freed from lipoids by extraction with ether and tested after removal of the ether.

b. One group of extracts was prepared in the same way with the only difference that blood was treated with heparine to prevent clotting, incubated for 15 minutes at 38° and then treated as under (a).

c. Same as (a) except for extraction with ethyl alcohol at room temperature.

d. The blood was treated with heparine and placed in a cellophane tube and dialyzed against destilled water in the cold for 20—48 hours. The outer fluid was concentrated to a few ml, methyl alcohol added to remove inorganic salts and prepared as under (a) except that ether extraction was omitted.

e. The blood was treated with heparine and the plasma centrifuged off. To the plasma the same volume of saturated ammonium sulphate was added and the precipitate filtered off, and dialyzed against running tap water for 48 hours in a cellophane tube. The contents of the tubing were precipitated with 3 volumes of ethyl alcohol, filtered, evaporated and taken up in water.

f. Heparine plasma was dialyzed and treated as (d).

g. Heparine plasma was precipitated with 3 volumes of alco ho and treated as (c).

h. Red cell concentrate, treated as (c).

i. Oedema fluid, collected from a scarification, treated as (c).

The majority of the separate samples of blood from cases with hypertension were treated according to (g).

k. The following method of preparation was finally adopted to the more extensive tests, in which the extracts corresponded to about 1 litre of pooled plasma. Plasma and blood corpuscles were treated separately and the plasma was either dialyzed or precipited directly with alcohol. The normal or hypertensive blood was in both series heparinized and collected in paraffinated vessels, and sharply centrifuged in paraffinated tubes. In the former case the plasma was dialyzed in 100 ml portions in the cold against 10 volumes of distilled water for 48 hours. The dialysate was neutralized with sulphuric acid and concentrated in vacuo to about 200 ml. The extract was then subjected to continuous extraction with ether for 3 hours at pH about 4 and for another 3 hours at pH about 10. The ethereal extracts were shaken with some 10 ml of water to which sodium hydrate and sulphuric acid were added respectively in amounts necessary to remove the water soluble acid or basic compounds from the ether. After this treatment the original extract was concentrated in vacuo at pH about 5 until salts precipitated from the solution. The salts were filtered off and 5 volumes of ethyl alcohol were added to the filtrate.

The precipitated material was filtered off and added to the previously obtained salts. The filtrate was freed from alcohol and evaporated under reduced pressure until 1 ml of the extract corresponded to about 50—100 ml plasma. The extract then still contained a fair amount of organic material, notably glucose, and some inorganic salts.

The contents of the cellophane dialyzing bags were precipitated with 3 volumes of alcohol, filtered and evaporated to a small volume. In some cases the blood corpuscles were precipitated with 3 volumes of alcohol and the extract, after evaporation of the alcohol, subjected to fluid extraction with ether at acid and alkaline reaction. The ether extracts were taken up in acid and alkaline water as above. The remaining extract was concentrated and treated as the plasma extract.

Assay of pressor activity in extracts of blood, plasma and dialysate of blood or plasma.

In order to obtain some kind of quantitative measure of the pressor activity we have used tyramine acid phosphate (B.D.H.) as a standard, referred to in the following as T.P., though we are well aware that there are notable differences in action and also in the relative sensitivity of the animal for tyramine and the pressor action of our extracts. In many cases the assay has allowed but a rather rough estimation, and in the later experiments the direct comparison of extracts of normal and hypertensive blood on the same animal was found to give more valuable information as to the quantitative effects.

The condition of the test animal was of great importance for the biological effect of the blood or plasma extracts. In general the best responses were obtained on healthy, not too young cats of about 3 kg weight. We have not found any definite favorable effect by using decerebrate or decapitate preparations as compared with animals anaesthetized with chloralose, provided that the anaesthesia was not too deep. A definite improvement was instituted by the use of a small dose of ergotamine tartrate (Gynergen) intravenously (0.05—0.1 mg pr kg). This dose did not diminish the effect of a test dose of adrenaline, but, on the contrary, not infrequently increased the pressor response. The same was the case for tyramine and the pressor effects in the blood extracts. The reason for this effect is probably the reduction or abolishment. of the pressor moderator reflexes from the carotid sinus and aorta as shown by the common carotid occlusion test (Euler and Schmiter- löw, 1944). We have adopted this treatment of the animal as a routine method in the latter part of the investigation. The pretreatment with ergotamine has also proved of value as a way to measure the general reactivity for pressor agents, as those animals which did not respond with a sharp rise in pressure on the injection of ergotamine generally reacted badly for the plasma extract pressor principle.

There has been no indication of tachyphylactic reactions in the test animals to the pressor action of the blood or plasma extracts.

Bohn has suggested that a previous depressor effect may modify or even cause a subsequent pressor action. In our experi-
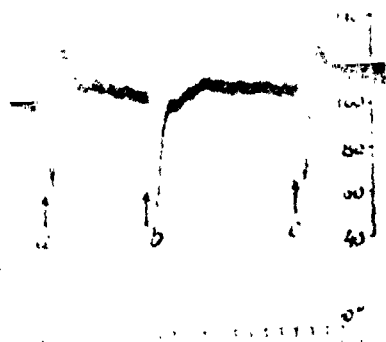
Fig. 1. Cat, chloralose, blood pressure. Alcoholic extracts of 25 ml plasma. a and c from patients with normal blood pressure, b from a case of essential hypertension.

ments an effect of this kind has probably been of little importance. Thus a slow injection of normal plasma extract with a very moderate lowering of the blood pressure has produced a stronger pressor effect than a fast injection of hypertensive plasma extract causing a markedly stronger depressor effect. In fig. 1 the pressor effects vary considerably though the foregoing depression is very nearly the same.

Results.

1. Alcoholic extracts and dialysates of blood or plasma.

The concentrated alcoholic extracts of normal or hypertensive blood and plasma on nearly all occasions showed some pressor activity preceded by a fall. The effect seemed to be identical whether alcohol was added at boiling point or at room temperature. In order to test whether the treatment with alcohol liberated substances causing the pressor effect we also tested the effect of dialysates from whole blood and plasma. Even in these cases, however, a pressor effect was regularly obtained with the concentrated extracts, corresponding to 10—100 ml blood. We can fully agree with Page, however, that the assay of the pressor action is difficult and we can claim no better results than Bohn as regards concentration and purification of the active substances. As a general result it was observed, however, that the pressor activity of extracts from normals was more potent than that from hypertensives, using alcoholic extracts as well as dialysates. This is illustrated by Fig. 1, 3, 4 and Tables I and II.
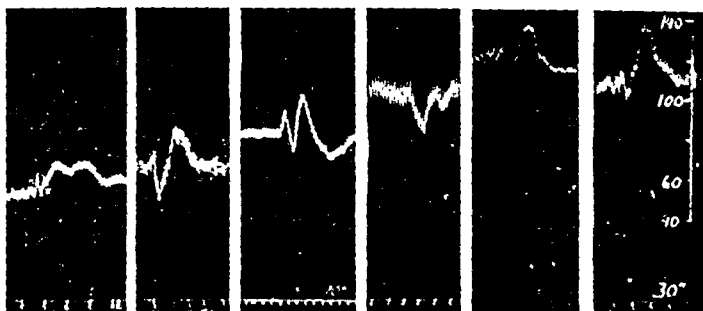
Fig. 2. Cat, chloralose, blood pressure. Various types of effects of extracts of normal blood or plasma. a 24 ml blood, b 9 ml blood, c 35 ml dialysate blood, d 25 ml dialysate plasma, e 20 ml same, f 20 ml blood.

In most experiments the rise of blood pressure after injection of plasma or blood extract from normal as well as from hypertensive subjects has been preceded by a fall in blood pressure. In a few instances only we have obtained a pure pressor effect. The type of action of normal blood extracts has varied within wide limits as illustrated in fig. 2.

The following methods have been employed in purifying the pressor principle from normal plasma.

Alcoholic extracts or dialysates have been evaporated to a small volume and treated with 4—5 volumes of methyl or ethyl alcohol at a slightly alkaline reaction (pH 8—9). The alcohol precipitated mostly inorganic salts which, when redissolved, had either a diphasic or no action or lowered the blood pressure. Most of the pressor action was found in the filtrate (Fig. 3). A precipitate with pure pressor action has been obtained when the filtrate after precipitation with 4—5 volumes of alcohol was acidified with H_2SO_4. The filtrate, taken down to dryness at low temperature and redissolved in a small amount of water gave about the same depressor effect as before and a slightly reduced pressor effect. When the extraction with alcohol was made at an acid reaction the pressor activity in the extract was smaller. Extraction with 3 volumes of acetone yielded similar results as those with alcohol. Addition of 3 volumes of ether to the alcoholic alkaline solution left only little of the pressor activity in the filtrate but gave in one occasion a pure pressor action in the precipitate. We have concluded from these experiments that the pressor principle is soluble in dilute alcohol
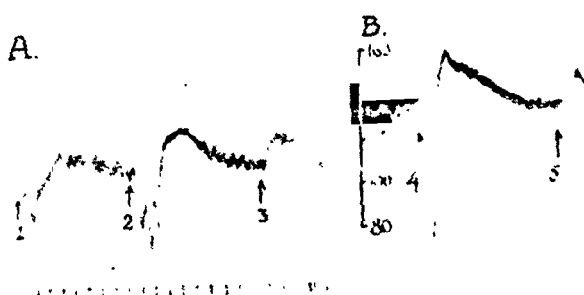
Fig. 3. Cat, chloralose, blood pressure.
    A. 1. dialysate of 50 ml hypertension plasma
       2. dialysate of 50 ml normal plasma
       3. 0.25 mg tyramine phosphate.

    B. after 0.25 mg ergotamine i.v.
       4. alcoholic extract of 50 ml normal plasma dialysate as above
       5. same from hypertension plasma.
    Time 30 sec.

but insoluble in ether. This is also supported by the results described below. The pressor activity was not destroyed by 10 minutes heating to 100° C at normal acid or alkaline reaction as shown by fig. 5.

In those experiments where pooled extracts of blood corpuscles and plasma from normal and hypertensive subjects were compared in the same animal the results were similar to those found when single tests were made.

Though the reactions showed no strict consistency on all occasions we feel justified in making the following statements.

    1. Plasma.

        a. Ether extract, alkaline.

           Normal: No depression, slight pressor effect (100—400 ml plasma) (Fig. 4 and 5).

           Hypertensive: No depression, slight pressor action, usually less than for normals. (Fig. 4).

        b. Ether extract, acid

           Normal: Slight pressor action (100—400 ml plasma) (Fig. 4 and 5).

           Hypertensive: Smaller effect than for normals.

        c. Alcohol extract after ether extraction

           Normal: Considerable depressor action, moderate pressor effect (50—200 ml plasma) (Fig. 4:6 and 5:4).
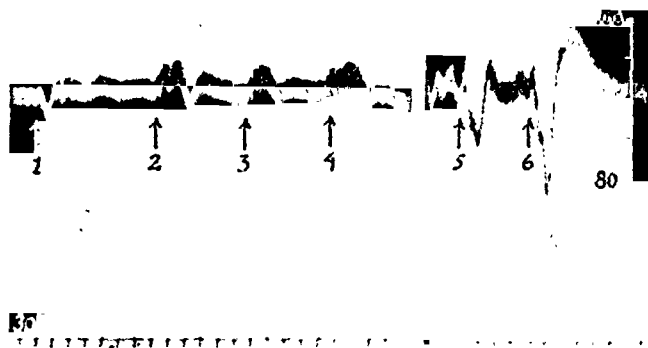
Fig. 4. Cat. chloralose, blood pressure.
1. acid ether extract of 200 ml hypertension plasma
2. acid ether extract of 200 ml normal plasma
3. alkaline ether extract of 200 ml hypertension plasma
4. alkaline ether extract of 200 ml normal plasma
5. alcohol extract of 100 ml hypertension plasma
6. alcohol extract of 100 ml normal plasma.

Hypertensive: Smaller depressor action, small pressor effect (Fig. 4).

2. *Blood corpuscles.*

a. *Ether extracts, acid and alkaline.*

Fairly large variations in response. Pressor effects slight or absent. Stronger depressor action in extracts from hypertensives (100—200 ml b.c. suspension).

b. *Alcohol extract after ether extraction.*

Pressor or depressor effects.

No constant difference between normals or hypertensives.

Though the pressor effect of extracts from plasma directly precipitated with alcohol was somewhat stronger than those prepared from dialysates of plasma the differences were not great and quantitative only.

The precipitated salts generally exercised a small pressor (plasma) or depressor (blood corpuscles) action (Fig. 5) which persisted after incineration, but this action was small as compared with that of the filtrate after removal of the salts.

The contents in the dialyzing bags, blood or plasma, were mostly inactive when tested after extraction with 3 volumes of alcohol.
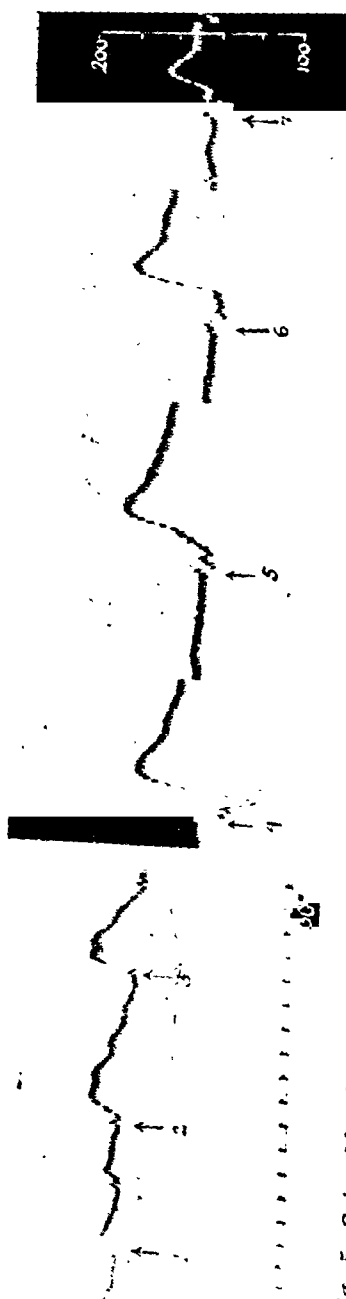
Fig. 5. Cat, chloralose, blood pressure, ergotamine, atropine.   Extracts of normal heparine plasma.
1. alkaline ether extract of 400 ml plasma
2. acid ether extract of 400 ml plasma
3. 0.1 mg tyramine phosphate
4. methyl alcohol extract of 50 ml plasma
5. same, treated with NaOH for 10 min. at 100°
6. Same, treated with n H_2SO_4 for 10 min. at 100°
7. salts precipitated with 20 volumes of alcohol at pH 9 from the same extract as in 4.

Survey of results with extracts of normal blood or plasma.

The results with normal blood or plasma are computed in Table 1.

Table 1.

a. whole blood extracted with boiling EtOH.

Nr.		Pressor action eqv. to mg T. P. per 100 ml blood
1. G. S.	♂	2.7
4. G. J.	♂	1.3
5. L. L.	♂	2.2
6. S. W.	♂	1.5
7. G. P.	♂	1.25
8. S. C.	♂	0.7
1—8 Collected extracts, reextracted with McOH		1.5

b. same as a. but incubated 15′ at 38° before treatment with EtOH

1. G. S.	♂	1.3
2. A. D.	♂	2.5
4. G. J.	♂	1.0
5. L. L.	♂	1.5
6. S. W.	♂	1.8

c. whole blood extracted with EtOH at room temp.

9. S. E. F.	♂	1.0
10. M. L. B.	♀	2.5
11. K. L.	♂	1.3
12. J. N.	♀	1.0

d. whole blood dialysate

7. G. P.	♂	0.5
8. S. C.	♂	1.2
10. M. L. B.	♀	1.2
11. K. L.	♂	1.3
12. J. N.	♀	1.0

e. plasma alcoholic extract

22. N. N.	♂	0.5
23. G. U.	♂	0.8
24. K. A.	♂	0.8
25. Collected from 5 medical students		0,8
26. Collected from 5 medical students		0.5

f. plasma dialysate

20. E. Ö.	♂	1.0
21. G. P.	♂	1.2
27. Collected from 6 medical students		0.5

g. oedema fluid alcohol extract   0.6

Survey of results with extracts of blood or plasma from hypertensives.

Table 2.

Nr	Name	Clin. diagnosis	B. P.	Remarks H = Heller	Preparation eqv. to mg T. P. per 100 ml
1	S. K. 1913 ♀	Hypert. ess. maligna	250/180	H: trace Norm. Kidney function.	Blood, dialysed 0.6
4	J. S. 1876 ♀	Aplasia ren. sin. c. hypertonia + anemia sec.	245/130	H neg.	Blood, alcohol 0.6 Blood, dial. 0.5
5	J. J. ♂	Hypert. ess.	250/150	H neg.	Blood, alc. 0.3
6	A. G. 1865 ♂	Hypert. ess. + cardioscl.	235/110	H neg.	Blood, dial. 0.5 Blood, dial. 0.3
7	G. H. 1898 ♀	Hypert. ess. grav.	290/160	H neg.	Blood, dial. 0.6
8	G. P. 1876 ♂	Hypert. ess. + arterioscl.	260/100		Blood. dial. 0.3
9	J. A. C. 1877 ♂	Hypert. ess. + cardioscl.	180/90	H neg.	Blood. dial. 0.5
10	E.I.T. 1900 ♀	Nephrit. chron. + acuta, retinitis hypert.	255/180	Esb. 4°/₀₀ single red b.c.	Blood. dial. 0.3
20	D. L. 1873 ♀	Nephrolithias. sin.	190/115	H pos. Red and white b.c.	Blood. dial. 0.6
22	E.M.L.1889 ♀	Hypert. ess.	250/135		Plasma dial. 0.9
23	J. L. 1869 ♂	Hypert. ess. + cardioscl.	220/125	H pos.	Plasma dial. 0.5
25	J.E.N. 1896 ♂	Hypert. + glom. nephr. chron.?	250/150	H trace	Plasma alc. 0.2
26	K.J.J. 1875 ♂	Hypert. ess.	220/110	H neg.	Plasma 0.2
27	J. N. 1875 ♂	Hypert. ess.+ card. scl.	230/130	H trace	Plasma 0.5
28	A. K. 1872 ♀	Hypert. ess.	240/120	H neg.	Plasma < 0.3
29	A. H. 1893 ♀	Hypert. ess. + insuff. cord. + climact.	250/130	H neg.	Plasma < 0.3
30	K. N. 1881 ♂	Hypert. ess.	230/110	H neg.	Plasma 0.3
31	E. K. 1870 ♀	Hypert. ess.	290/140	H neg.	Plasma 0.3
32	K.H.N.1881 ♂	Hypert. ess.	240/120	H neg.	Plasma 0.3
33	G. L. 1863 ♂	Hypert. ess.	240/120	H pos.	Plasma 0.3
35	A.M.L.1872 ♀	Hypert. ess. + cardioscl.	295/150	H. neg.	Plasma 0.6
36	E.M.S. 1870 ♀	Hypert. ess.	270/150	H neg.	Plasma 0.3
37	P.J.M.1866 ♂	Hypert. ess.	210/110	H neg.	Plasma 0.4
38	H.C.J. 1871 ♀	Hypert. ess.	265/150	H neg.	Plasma 0.6

Nr	Name	Clin. diagnosis	B. P.	Remarks H = Heller	Preparation eqv. to mg T. P. per 100 ml	
39	T. G. K. 1887 ♀	Hypert. ess.	240/160	H neg.	Plasma	0.4
40	O. S. H. 1893 ♀	Hypert. ess.	270/155	H neg.	Plasma	0.6
41	E. M. T. 1893 ♀	Hypert. ess.	290/160	H trace	Plasma	0.4
42	L. M. J. 1885 ♀	Hypert. ess.	300/150	H pos.	Plasma	0.4
43	G. G. H. 1899 ♂	Hypert. ess.	210/140	H neg.	Plasma	0.4
44	S. G. Ö. 1875 ♀	Hypert. ess.	300/140	H neg.	Plasma	<0.3
45	N. K. E. 1896 ♂	Nephrit. chron. + hypert. + nephro-sclerosis	175/120	H pos.	Plasma	0.4
46	H. H. 1870 ♀	Hypert. ess.	245/180	H neg.	Plasma	0.5
47	S. K. H. 1887 ♀	Hypert. ess.	270/135	H neg.	Plasma	0.5
48	J. N. 1875 ♂	Hypert. ess.	220/120	H neg.	Plasma	0.5
49	K. C. B. 1881 ♀	Hypert. ess.	260/135	H trace	Plasma	0.3
50	M. J. E. 1891 ♀	Hypert. ess.	205/110	H neg.	Plasma	0.3
51	J. A. 1887 ♂	Hypert. ess.	285/165	H neg.	Plasma	0.3
52	S. O. 1884 ♂	Hypert. ess.	220/120	H pos.	Plasma	0.4
53	F. F. 1870 ♂	Hypert. ess.	280/100	H neg.	Plasma	0.4
54	A. H. S. 1870 ♂	Hypert. ess.	200/110	H neg.	Plasma	0.2
55	A. S. 1864 ♀	Hypert. ess.	300/?	H neg.	Plasma	0.4
56	E. N. 1869 ♀	Hypert. + diab.mell.	260/150	H neg.	Plasma	<0.2
60	H. K. A. 1865 ♀	Hypert. ess.	265/125	H pos.	Plasma	0.8
61	B. K. 1888 ♂	Nephrit. chron. + hypert.	280/150-60	H pos.	Plasma	0.2
63	E. H. M. 1888 ♀	Hypert. ess.	200/190	H neg.	Plasma	0.8
67	1891		295/170	H neg.	Plasma	0.4
68	I. S. J. 1881 ♀	Hypert. ess.	260/120	H neg.	Plasma	0.6
69	G. G. H. 1891 ♂	Hypert. ess.	200/130	H neg.	Plasma	0.8
72	E. S. G. 1896 ♂	Hypert. ess.	230/120	H pos.	Plasma	<0.4
73	B. S. A. 1881 ♂	Hypert. ess.	245/115	H pos.	Plasma	0.6
74	A. K. H. 1886 ♀	Vitium org. cord.	220/120		Plasma	0.5
75	Collected from 5 patients with essential hypertension					0.3
76	Collected from 5 patients with essential hypertension					<0.3

2. Tests for renin, hypertensin (angiotonin) and hypertensinogen.

Though no evidence has been obtained for the presence of hypertensin in our blood samples — the pressor activity being insensitive to treatment with hot alkali — we have for the sake of completion made a few tests for the presence of renin, hypertensin and hypertensinogen. Extraction with 3 volumes of alcohol direct-

ly and after 15 minutes incubation at 38° gave the same yield in pressor activity. After dialysis of heparinized whole blood renin was added in an amount known to produce a maximal hypertensin formation and incubated for 15 minutes at 38°. After coagulation of the proteins with hot alcohol and evaporation of the alcohol the extract showed the expected additional pressor activity, amounting to about 0.3—0.5 mg T.P. per 100 ml of blood. We have not been able to find any consistent difference in the amount of extra pressor activity formed with blood from normal subjects and from hypertensive patients. The fact previously reported, that extracts of normal blood produces a greater pressor effect than those of hypertensive blood also seems to point in a negative direction as to a possible increase in the amount of hypertensin, renin or hypertensinogen.

When a crude hypertensin (angiotonin) preparation was added to 200 ml heparinized blood and dialyzed for 24 houis in the cold through cellophane, about one half of the added pressor activity was resovered, using the routine method (g) of extraction. Incubation for 15 minutes at 38° after addition of the pressor agent did not sensibly reduce the yield, showing that it is not destroyed by blood during this time.

With regard to the possibility of active off-splits from globulines appearing as a result of alcohol treatment we have prepared globulines from normal plasma and extracted them with alcohol. The extracts were inactive.

Discussion.

Most previous investigators who have reported the presence of pressor activity in extracts of blood or plasma have found greater amounts in blood from hypertensives, especially in those cases which correspond to the pale hypertension of Volhard. Some authors, however, also found such activity in blood from patients with essential hypertension, but, so far as we are aware, only Page (1935) has pointed out that pressor action may be obtained from alcoholic extracts of normal plasma and other liquids of the body, such as ascites and liquor, to an even greater extent than in blood from hypertensives. According to this author the pressor principle

does not appear in ultrafiltrates but is liberated when the colloids are coagulated with alcohol. In our experiments, however, it was obtained also in dialysates from whole blood or plasma. We consequently do not believe, that physico-chemical disturbances are necessary to liberate the agent, which seems to occur in a »free» state.

When whole blood, heparinized or not, was used for alcoholic extraction, the amount of pressor activity was on an average higher than when plasma was used. This points to the presence of greater amounts of pressor activity in the red blood cells which also could be shown directly in some cases. On the other hand the red cells seemed to contribute to the depressor action of the extracts, though this was rather varying, partly depending on the reactivity of the test animal. We have gained the general impression that the depressor action of normal plasma extracts have been more marked that that of our hypertensive material.

As to the nature of the pressor agent in normal blood and plasma rather little can be stated as yet with certainty. It is soluble in alcohol, but may be precipitated from an alcoholic solution with ether. It cannot be extracted with ether from an aqueous solution either at acid or alcaline reaction. It is dialysable and resists heating to 100° for 10 minutes in normal alkaline or acid solution. Its action is not increased by cocaine in the cat under chloralose. Thus it can be stated with a fair degree of accuracy that it is not identical with adrenaline, tyramine, oxytyramine, iso-amylamine or hypertensin. Before any further statements can be made it is necessary to find methods for concentrating the active principle and prepare it in greater amounts.

The significance of our finding that in normal blood and plasma extracts the pressor activity is on an average stronger as compared with the corresponding extracts of blood from hypertensives is not clear. It is only natural, however, to correlate this finding with that of pressor agents in normal and hypertensive urine, where a similar difference is noted, as described in a following paper, though the active substances in the latter case are of a different kind.

Summary.

Alcoholic extracts of normal blood and plasma usually give a pressor action, preceded by a depressor action, on the cat under chloralose.

Dialysates of normal blood and plasma produce similar effects. The pressor agent is soluble in dilute alcohol, insoluble in ether, thermostable and dialysable. Its action is not influenced by cocaine.

In blood or plasma dialysates and extracts from patients with essential hypertension the pressor activity was not higher than in extracts from normals. In our material the pressor activity was, on the contrary, less in extracts from hypertensive blood, including 4 cases of chronic nephritis.

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Isolation and Individual Nursing of Scarlet Fever as Compared with Nursing in General Wards.

By

ROLF BERGMAN.

(Submitted for publication June 20, 1944.)

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»Individual consideration of the patient is an accepted fundamental of good clinical management of scarlet fever». (Gordon J. A. M. A. 1932 Vol. 98 p. 519).

The truth of this rule does not seem to have been realized in Sweden as yet. An antiquated routine is followed, which is not least conspicuous when determining the nursing time. I have previously had occasion to emphasize the importance of individual nursing in view of the nursing time, especially considering the frequency of return cases. I now insist upon it that this principle be given due consideration also in the arrangement of the hospital nursing.

It is comparatively easy to individualize the duration of the nursing time, it merely being necessary to devote sufficient attention to each patient and to allow adequate time for the examination when the discharge of a patient is being comtemplated. As I have earlier demonstrated on Stockholm material [1], this results in great advantages for the infectious-diseases hospitals, not least from an economic point of view, and also lessens the patient's burden in scarlatina. An individualization of the nursing puts the staff and the premises to far severer tests. If consideration is to be paid to all differences in the course of the disease, the doctor and the

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[1] Nordisk hygienisk tidskr. 1942: 23: 375.

nurse must be capable and vigilant, in other words competent and trained, especially in the treatment of infectious diseases, and they must be able to spend sufficient time over each patient, so that he can be followed medically from his admittance to his discharge. This of course requires the employment of sufficient and sufficiently trained personnel and is thus an economic question.

If the nursing is to be individualized, it is also necessary, however, that the large composite units of patients be broken up and the large general wards abandoned. The scarlet fever patients must be divided into numerous small groups or each patient must even be nursed in a special room. This will make it possible to separate fresh cases from older ones, complicated cases from cases without complications, the various complications from each other, etc.

The idea of nursing scarlet fever cases in small groups, *i.e.* to avoid mixing cases that are mutually dissimilar, is not at all new, but its realization has so far been impossible in Sweden or in any case it has been rendered very difficult owing to the fact that our infectious-diseases hospitals are not planned and organized for such nursing. I therefore consider it all the more urgent to demonstrate and emphasize the actual advantages of such nursing and thus to influence my fellow-doctors and the authorities, so that we may be better equipped in the future.

It is an old experience that nursing in small units reduces the number of complications in the case of infectious diseases. This experience is not limited to scarlet fever, it having been demonstrated in the measles, *e.g.* by Debré-Joannon[1], and in other diseases. Complications are very prominent in scarlet fever. In the mild form of scarlatina which now occurs in middle and western Europe, in America and in the Scandinavian countries, practically the whole mortality is due to the complications, especially to the invasive ones such as otitis, infections in the maxillary sinuses and processes descending into the respiratory organs. The complications make the nursing more complicated, increase the work of the staff, increase the demands on medicine and surgery, and prolong the stay in hospital. Complications that have not healed completely when the patient leaves the hospital increase the risk of return cases[2], and cases that have suffered from complications

[1] La rougeole, Paris 1926.
[2] Gordon J. A. M. A. 1932: 98 p. 519 *et al.*

stance naturally somewhat affects the purity of the investigation» — but these influences will nevertheless have been fairly moderate. His results will be found in Table I. Out of the 171 cases nursed individually — 9 were excluded as they had received scarlatina convalescents' serum — 10 ₍6 per cent) experienced relapses, and out of 171 control cases 21 (12 per cent) experienced the same complication. Out of 152 cases originally without complications and nursed individually, 12.5 per cent had complications, and out of the 152 control cases almost 4 times as many = 45.4 per cent. A high fever as well as local complications, most especially lymphadenitis and otitis, were far more common among the control cases nursed in general wards. — This also affected the frequency of the return cases, it being 2.5 per cent in the case of those nursed individually and 5.5 per cent for the control cases.

Lépechin (cit. Hottinger) reports a similar experience. Among his patients nursed in hospital he had 37.1 per cent of return cases and among those nursed individually in their homes 7.6 per cent.

My own investigations.

These have been arranged along the same lines as Lichtenstein's and were intended partly to test certain of Lichtenstein's results, partly also to determine numerically what may be the influence of individual isolation upon the duration of the nursing time. The nursing time is a decisive factor in the nursing costs, an important matter from an economico-administrative point of view, and of great practical importance for the patients themselves.

The isolation was arranged in the same premises as were used by Lichtenstein, but it was stricter, as it was possible for me in each case to arrange for completely individual nursing during the whole stay in hospital. The staff of this department was controlled daily to make sure that there were no symptoms of infections in the throat and nose, and the least signs of catarrhal pharyngitis, angina, etc., being noticed, the person in question was suspended from the further discharge of his duties in the department. A continuous bacteriological control ensured that persons in which haemolytic streptococci could be demonstrated were removed from the department.

The material consisted of 200 cases of fresh and typical scarlet fever, without complications, just received into the observation department of the hospital. They had no contact with other patients before the experiment was started. 100 of the cases were selected for individual isolation and for each such case the patient most closely corresponding to it with reference to time of admittance, age, sex (in adults), and the severity of the disease was selected as a control case. Also the control cases were devoid of complications when admitted. The control cases were transferred from the observation department to a general ward, where they remained during the whole nursing time. The two groups were treated quite alike as regards the daily nursing and medical control, tests, special examinations, the principles of discharge, etc.

That the two groups were judged alike as regards the severity of the cases would appear to be demonstrated by the fact that the number of cases requiring scarlatina serum was about the same, 12 in the group nursed in a general ward and 15 in the individually isolated group.

The material has been tabulated according to the various complications, and some of them, those that may be assumed to be due to an invasion of haemolytic streptococci in the respective organs, have been grouped together under the heading »Septic complications», and others, which may be assumed to be due to toxic agents, under the heading »Toxic complications». A question that might be discussed is whether the very common cases of lymphadenitis — most frequent in the throat — are septic or toxic; in the table now presented they are grouped as septic. — Relapses, return cases, and the duration of the nursing time have also been tabulated. The table further states when the patient has been given serum (convalescents' serum) and if he has been given sulfanilamid (chemotherapy).

The various data will be found in Tables 1 and 2.

The whole material is first accounted for in Table I. It is there compared with my own very thoroughly examined material for the years 1938/39. This latter consists of 3495 typical fresh cases. Parts of the investigation have earlier been published in *Nordisk hygienisk tidskrift* 1941 and 1942. This material shows the frequencies of the various complications that may be considered typical of present-day scarlet fever when the patients are nursed

in general wards. — The table also contains Lichtenstein's figures obtained in a similar investigation carried out in 1931 (*l.c.*).

In both series a number of bacteriological examinations were also made, especially to ascertain the occurrence of haemolytic streptococci in the various stages of the disease. These examinations were carried out in collaboration with Dr A. Ehinger, who will be publishing the results in another connection.

In Table 2 some of the results have been subjected to a further analysis.

Table 2.

	Nursing		
	In a general ward	Individ.	Difference
Without complications	32±4.7	51±5.0	19±6.8
Number of septic complications	67±4.7	48±5.0	19±6.9
Number of patients with septic complications	58±4.9	41±4.9	17±7.0
Number of toxic complications ·	17±3.8	18±3.9	1±5.4
Chemotherapy	38±4.9	14±3.5	24±6.0
Return cases	4±2.0	1±1.0	3±2.2

Out of the 100 cases that were nursed individually only 49 had any complication at all, while 68 of the control cases developed complications. The difference is statistically significant. Lichtenstein's figures give the same picture.

Conditions are not the same, however, with regard to the invasive »septic« complications produced directly by the streptococci and the »toxic« complications assumed to be due to toxin. In the control series there were 67 »septic« (sometimes the same patient had several complications) and but 17 »toxic« complications. For the individually isolated cases the figures were 48 and 18 respectively. As regards the »septic« complications, the difference of 19 is statistically significant, and if, as has been done in Table 2, a comparison is made not between the number of complications but between the number of patients overtaken by »septic« complications, the same result is arrived at, a nearly statistically significant difference between the two series — 58 and 41 respectively. The number of toxic complications, however, is practically the same in the two series. ·

The more frequent use of sulfanilamid remedies in the group nursed in a general ward is also a sign of the septic complications being more common and undoubtedly often more alarming in that group. The indications for chemotherapy were of course the same. In the control series chemotherapy was made use of for 38 patients, in the individually isolated series for but 14 patients, which gives a statistically significant difference (Table 2).

The investigation has thus confirmed the earlier conception that individual isolation protects the patient better against the invasive streptococcus complications in scarlet fever. The cause of this is not demonstrated by the material now presented, but the modern theory on the importance of the various types of streptococci might explain it. According to that theory the patient might be infected by the streptococci of his fellow-patients. It is evident, however, that even the very careful isolation now considered, in which the staff was also subjected to strict control, does not provide a one-hundred-per-cent protection against such complications.

Relapses have most especially been attributed to exogenic infections, *i.e.* to infections from fellow-patients with a type of streptococci different from those of the patient himself. The findings in this investigation, no relapses among those nursed in individual isolation and 4 in the control series with its possibilities of exogenic infections, seem to support that opinion.

The investigation also included a control of which cases gave rise to return cases after their return home. It was disclosed that no less than 4 of the cases belonging to the control series were infecting cases, which makes a frequency of return cases exceptionally high for the hospital. Three of these cases had septic complications during their stay in hospital, two otitis and one angina; the fourth had had synovitis. — The nursing time was long for these four infecting cases, 6 weeks and more. Among the cases nursed individually there was only one infecting case. He had been nursed for 33 days, had suffered from lymphadenitis while in hospital but had no symptoms whatever when discharged.

One of the aims of the investigation was to study the influence of the nursing conditions on the nursing days. The values obtained will be found in Table 3.

Table 3.

Number of cases	Individual isolation	Control series
	100	100
	Mean nursing time — days	
Arithmetic mean	35.4±1.21	43.5±1.97
Lower quartile (P 25)	29	30
Median (P 50)......................	31	37
Upper quartile (P 75)	38	54

As might be expected in view of the smaller frequency of complications and relapses the individually isolated series had the shorter mean nursing time, 35.4 days as compared with 43.5 days for the control series. The difference between these two means is 8.1±2.3 and is thus statistically significant. The medians (see Table 3) also definitely indicate this to be the case.

The benefit of this is not inconsiderable. Apart from what it means for the patients themselves, it implies a smaller number of patients in hospital and a smaller number of nursing days. A financial calculation based on the number of nursing days shows that a reduction of the nursing time by 8 days and with an estimated nursing cost of 10 Swedish kronor per nursing day (a low estimate at the present time) results in a gain of 8,000 kronor per 100 cases annually. This gives an idea of what enormous sums are involved considering the tens of thousands of cases we have every year in Sweden.

Summary.

100 fresh and typical scarlet fever cases were subjected to individual isolation during their whole time in hospital. As control cases there were selected patients corresponding to each of the above-mentioned cases with reference to age and clinical data. The control cases were nursed in an ordinary general ward during their whole stay in hospital.

The investigation showed

1) that the number of »septic« complications — otitis, infections in the throat and respiratory organs, impetiginous skin processes

and lymphadenitis — were decidedly fewer among those isolated individually than in the control series;

2) *that the »toxic» complications were equally common in the two series;*

3) *that relapses only occu·red in the control series;*

4) *that the frequency of return cases ·(infections) was 4 times as high in the control series as in the individually isolated series; and*

5) *that the mean nursing time was 8.1 days shorter for the cases isolated individually than for the control cases nursed in a general ward.*

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Tissue immunity in mouse poliomyelitis.[1]

By

SVEN GARD.

(Submitted for publication August 2, 1944).

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Up to the present substantial evidence concerning the nature of tissue immunity is very scarce. Generally the phenomenon is attributed to antiviral substances in the interior of the cells, acting fundamentally as neutralizing antibodies. As tissue culture experiments have revealed the inability of antiserum to exact any influence on the course of infection once the invasion of the cells has occurred, the »autosterilization» of the tissue is explained by the assumption of such intracellular antibodies developing as a result of the interaction between virus and host. They are called »sessile» as distinct from the »mobile» antibodies of the blood.

As, generally, tissue immunity is associated with a high neutralizing serum titer its existence is not always easily demonstrable in vitro. It has been possible, though, in studies on the development of immunity during the early stages of infection, to demonstrate an isolated tissue immunity. For instance, Ørskov (1) was able to show that testicular tissue after intratesticular inoculation of vaccinia virus exhibited definite antiviral properties at a time when antibody had not yet appeared in the blood. In such cases the tissue in question is considered to be the site of antibody production. The mobile antibodies are merely liberated from the tissue. Sometimes, in rabbits immunized against Herpes or Borna disease,

the presence of antiviral substances has been found to be restricted to the brain and, possibly, the adrenals, whereas the blood is devoid of neutralizing substances (2, 3, 4).

It is quite natural that tissue immunity should play an important part in the development of the general immunity in virus diseases in particular, on account of the intracellular »parasitism». This latter fact, however, necessitates a scrutiny of the problem from a different angle. There has been a trend to explain the cellular immunity in virus diseases such as vaccinia as dependent upon the persistence in the tissue of active virus. The entrance of new virus particles into a cell already containing the same virus is assumed to be blocked, the cell »receptors» to be saturated. Thus, the cell is protected against superinfection. When the receptors for different strains of virus are identical, the phenomenon of »interference» occurs. Magrassi (5) found that intracerebral inoculation in a rabbit of encephalitogenic Herpes virus, otherwise regularly causing a lethal infection, was quite innocuous if the animal had obtained a corneal inoculation of an ordinary non-neurotropic Herpes strain a few days previously. The latency period necessary was too short to account for the development of an immunity of the usual type but long enough for the transition of the virus from the eye to the brain. In this case the »immunity» of the animal to Herpes encephalitis was obviously associated with the presence in the brain of the non-neurotropic form of the virus.[1] On the whole, non-neurotropic and neurotropic strains of the same virus often seem to interfere. As an example of interference of an inverse type Theiler's (6) confirmation and extension of Hoskins' (7) observation on yellow fever might be mentioned. Theiler's experiments were concerned with an ordinary viscerotropic strain of the virus and the »mutated» neurotropic (yellow fever vaccine) strain. He found that monkeys inoculated intraperitoneally with visce otropic virus, otherwise promptly succumbing to the infection, did not only survive but failed to show any demonstrable symptoms of yellow fever if a certain amount of neurotropic virus had been added to the inoculum. The decisive factor for the outcome of the experiment was the proportion of neurotropic to viscerotropic, not the absolute quantity

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[1] The Magrassi phenomenon might perhaps as well be regarded as an example of »Schienenimmunität» (Doerr).

of viscerotropic virus. — Sometimes interference between different viruses has also been observed as between Rift Valley fever and yellow fever (8), lymphocytic choriomeningitis and poliomyelitis (9), or vaccinia and foot-and-mouth disease (10).

Jungeblut and Sanders (11) working with the murine SK strain of poliomyelitis virus describe a phenomenon interpreted by them as interference. Passage of the simian strain through cotton rats to white mice was regularly accompanied by a complete loss of pathogenicity to monkeys, although the virulence proved to be extremely high in tests on mice. Jungeblut and Sanders observed, however, that intracerebral injection in monkeys of a suspension of brains from infected mice, made simultaneously with or before a test inoculation with a highly active simian strain, inhibited the development of typical symptoms. They found, furthermore, that the mouse virus exhibited the same effect when given intravenously on the condition that the application preceded the test inoculation.

The present writer (12) working with the purification of mouse poliomyelitis virus was not able to demonstrate interference in the above sense of the word between purified virus preparations of different pathogenicity. On the contrary, when a purified preparation of fecal myelitogenic virus of low virulence was added to the encephalitogenic and highly active FA strain an enhancement of the virulence resulted. The admixture of the purified fecal virus had the same effect as would an additional amount of the FA virus itself. Thus, an »interference» occurred but of a type opposite to that described above. The FA virus induced a high virulence and encephalitogenic properties in the ordinarily rather harmless fecal strain. On the other hand, when a crude brain suspension of a fecal passage strain was mixed with FA virus, the development of encephalitic symptoms was inhibited and the attack rate considerably lower as compared with control groups, in accordance with Jungeblut's observation. The results of these experiments considered together suggested that the protective action was not exhibited by virus of low virulence, but due to the presence in the crude brain extracts of one or more specific inhibitors. This assumption was further corroborated by the following observations. A crude brain suspension was subjected to differential centrifugation and divided into three fractions, one containing debris and coarse material, another consisting of macromolecular soluble substances, and

finally one containing low-molecular, non-sedimentable material. The virus content of each fraction was determined by means of activity measurements. It was found that the total yield of virus with approximately 40 p.c. exceeded the virus content of the original suspension, as calculated from its activity. Furthermore, after digestion of a brain suspension with pancreatic juice the virus activity was found to be 4 times that of the control. The increase in activity in the latter case could be explained by a liberation of virus from the digested cells but in the former case no such explanation holds true. One would rather expect an agglomeration of virus particles with a decrease in activity as result. The most plausible explanation is that the crude suspension contains inhibitors which, owing to differences in molecular weight, can be separated from the virus by means of centrifugation and are destroyed by digestion with pancreatic juice.

As this phenomenon seems to offer possibilities of the elaboration of prophylactic measures against poliomyelitis it was deemed necessary to subject it to further studies. Some preliminary results are presented below.

Material and methods.

For immunization purposes the following strains of virus were used: U I F, a fecal strain isolated from a stock mouse showing spontaneous paralysis of the hind legs; U II F, likewise a fecal strain isolated from a healthy stock mouse; U V N, isolated from the spinal cord of a spontaneously paralyzed stock mouse. All strains were propagated by cord to brain passages in mice. Each of them displayed a considerable stability with regard to the length of the incubation period which was as an average 14, 12.5 and 8 days respectively. As a test strain Theiler's FA virus was used.

Brains of immune mice were ground with sterile sand and saline. After settling of the sand the turbid suspension was decanted. Equal parts of the suspension and clarified FA extracts were mixed and inoculated intracerebrally in 0.02 ml amounts into Swiss mice, 4 weeks of age. At least ten mice were used to each test. The viral activity of the preparations was assayed according to the principles laid down in previous papers [12]. Thus, symptoms and incubation periods were recorded and the activity calculated from the formula $y = S (1/t)$: n, t denoting the individual incubation periods and n the number of mice in the test.

The inhibition phenomenon.

In preliminary experiments it was found that normal brain suspension when added to FA virus had no effect on the activity except that of mere dilution. As a rule such normal controls were included in the experiments to be described below but as they never differed significantly from the saline controls they will be omitted from the tables.

Immune brain without demonstrable quantities of active virus gave very straightforward results. A number of mice were inoculated with UIF. Surviving animals received a test dose of FA virus 4 weeks after the first inoculation. All mice showing paralysis proved to be immune. After a further 4 weeks the animals were killed with chloroform and the brains prepared with saline to a 10 p.c. suspension. This was mixed with varying concentrations of FA virus. A corresponding control series contained saline instead of immune brain suspension, and furthermore an activity test on the original brain suspension was included. All mixtures were inoculated immediately into 10 mice each. Table I and Fig. 1 contain the results of two such experiments. The figures refer to the activity expressed as $y = S (1/t):n$.

Table I.

Conc. of FA	Experiment 1		Experiment 2	
	Immune brain	Control	Immune brain	Control
10^{-3}	0.117	0.230	0.107	0.215
10^{-4}	0.057	0.170	0.078	0.146
10^{-5}	0.014	0.101	0.045	0.107
10^{-6}	0.000	0.029	0.004	0.046
Control	0.000		0.000	

It is evident that admixture of immune brain diminishes considerably the activity of FA virus. It was previously shown (12) that the activity, y, varies rectilinearly with the logarithm of the concentration of virus. The graphs in Fig. 1 show that the points of the FA control fit tolerably well to straight lines. It is an interesting fact that the same holds true for the mixtures of FA with immune brain.   In comparison with the controls these lines are

dislocated downwards and to the left and in addition they have a significantly flatter course. This kind of dislocation was previously found to be characteristic of an increased resistance in the test animals.

The protecting effect decreased rapidly with the concentration of immune brain. It was still demonstrable if the brain suspension was diluted 1: 10 whereas dilutions of 1: 100 gave results that did not differ significantly from the control. By simultaneous varia-
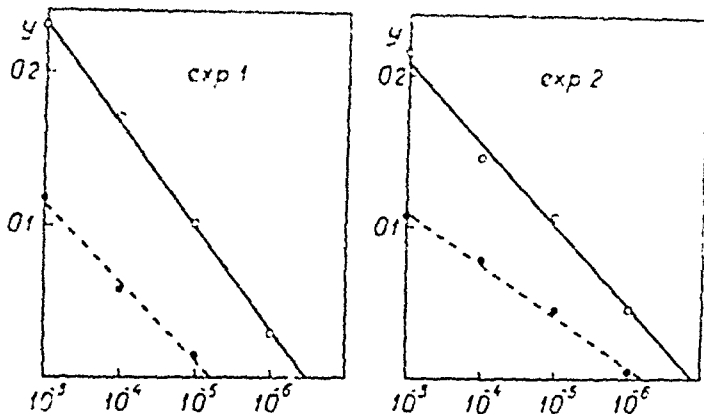
Fig. 1. Activity curves
Ordinate ~ y. Abscissa ← concentration of FA virus. Full line: FA control
Dotted line: FA + immune brain.

tion of the concentrations of immune brain and virus an interesting phenomenon was observed. One such experiment is tabulated in table II.

Table II.

Conc. of FA	Conc. of immune brain	y	
		test	control
10^{-3}	10^{-1}	0.107	0.215
10^{-4}	10^{-2}	0.131	0.146
10^{-5}	10^{-3}	0.106	0.107

The result is illustrated graphically in Fig. 2. Thus, if the original mixture of virus and immune brain is diluted the activity increases, passes through a maximum and then again decreases. This is a phenomenon of the same type as can be observed in par-

tially neutralized mixtures of virus and immune serum. In the latter case it is attributed to a dissociation of the virus-antibody compound.

Often the CNS of immune animals contains a considerable amount of biologically active virus. In those cases the activity assay is rendered more difficult. As, however, the test virus almost invariably causes an encephalitis with typical convulsions as the main symptom and the strains used for immunization give rise to
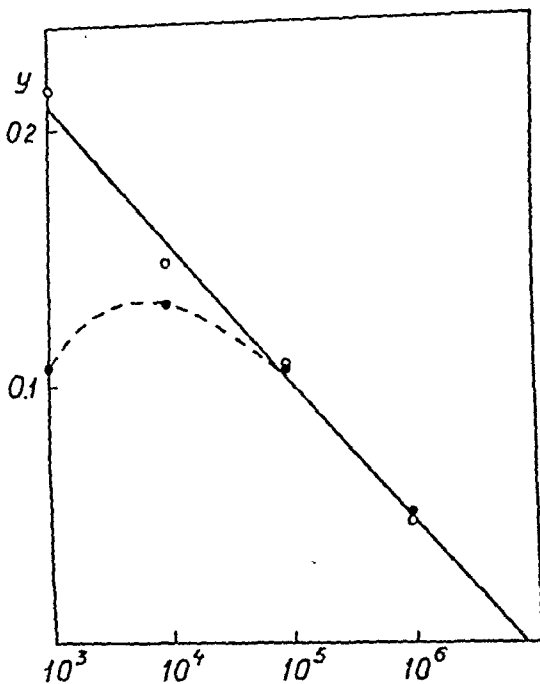
Fig. 2. Activity curves.
Full line: FA control. Dotted line: FA + immune brain.

a myelitis it is usually possible to distinguish clinically between the infectious agents. The etiological diagnosis can be further verified by means of passages. An example is given in table III.

Figures without brackets refer to animals showing typical encephalitis. Figures within brackets denote paralyzed mice without any traces of convulsions. Passages from such animals revealed the presence of the myelitogenic strain with the characteristic long incubation period. The plain brain suspension, without addition of FA virus paralyzing 9 out of 10 mice, contained obviously a considerable quantity of active virus. Nevertheless, it inhibited significantly the activity of the FA virus added. In attempts to

Table III.

	Conc. of FA	No. of mice	No. of animals showing an incubation period of days																				y obs.	y corr.
			3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	∞		
Immune brain	10^{-2}	10		1		4	5																0.163	0.163
	10^{-4}	10				1	1		1	3	2	1				(1)							0.105	0.099
	10^{-6}	10														(3)	(1)	(2)	(1)	(1)	(1)	2	0.049	0.009
	—	10												(1)(1)	(1)(1)	(1)			(3)		(1)	1	0.052	0.000
Saline	10^{-2}	10	4	4		2																	0.267	
	10^{-4}	10			1	4	3	2															0.155	
	10^{-6}	10						2	1			2					1					4	0.059	

express this inhibition numerically it seems to be justifiable to exclude the paralyzed animals not carrying FA virus in calculating the y values. The column headed y corr. contains the values arrived at in this way. It was generally found that the corrected figures gave a straight line of regression in accordance with those in Fig. 1, which was taken as evidence that this method of calculation was justifiable.

The time factor.

In several experiments the mixtures were tested immediately and after standing for different periods of time at room temperature or in the refrigerator. On no occasion any influence of storage was demonstrable. The inhibitory effect was developed to its full extent immediately after mixing.

Attempts at fractionation of the brain suspension.

15 immune mice were killed with chloroform and the brains triturated with sand and 50 ml of saline. The suspension was run »up-and-down» to 16,000 r.p.m. in a Beams' centrifuge. The heavy precipitate was resuspended in saline to a final volume of 25 ml. The supernatant was further run at 27,000 r.p.m. for 90 minutes. The second supernatant was removed and the precipitate was resuspended in 50 ml of saline. Thus, the preparation was separated into three fractions: a = debris and coarse material in twice the original concentration, b = macromolecular soluble substances, and c = low-molecular material. Each fraction was tested for protective effect. The results are collected in table IV.

Table IV.

Conc. of FA	a		b		c		Control
	obs	corr	obs	corr	obs	corr	
10^{-2}	0.062	0.039	0.163	0.163	0.153	0.153	0.267
10^{-3}	0.050	0.000	0.105	0.099	0.093	0.093	0.155
10^{-4}	0.046	0.000	0.049	0.009	0.031	0.031	0.059
Control	0.057		0.052		0.000		

The corrected and weighted y values of the row 10^{-2} are $a = 0.039$, $b = 0.167$, $c = 0.153$, and control $= 0.264$. These can be transformed to log MID (minimal infective doses) as previously described (12) and then give the following values $a = 0.25$, $b = 2.21$, $c = 1.94$, and control $= 4.08$. Hence, with this concentration of FA virus fraction a reduces the activity to 1: 21,400, b to 1: 74 and c to 1: 138.

Fractions a and b both contain active virus, a probably a little more than b, whereas c seems to be virus-free. The protective power of fraction a is about 300 times that of b with approximately the same virus content, and fraction c with no virus at all yet affords twice as good a protection as b. Obviously the inhibitory effect stands in no relation to the virus content.

Until the quantitative relationships of this inhibitory system have been subjected to a closer study it is impossible to compare the effects of the different fractions on an exact numerical basis. It is, however, quite evident that the major part of the inhibiting substances remains in the tissue debris. Olitsky (13) found that normal adult mouse serum contained neutralizing substances for Theiler's virus. I have been able to confirm this observation. Probably on account of this fact saline extracts of various organs exhibit a certain inhibitory action. The protection afforded is of the same order of magnitude as that of fraction c in the above experiment. It is likely, therefore, that the soluble fraction of the inhibitors of immune brain originates from the blood.

Repeated attempts to extract the tissue bound inhibitor with distilled water or saline solutions have failed. So far it has not been possible to obtain it in a soluble form. As a reason for this the possibility was considered that the degree of tissue disintegration after mere trituration with sand was insufficient. The material was, therefore, passed several times through a colloid mill (»homogenizer»). On microscopical examination of the final product no intact cells could be found although part of the nuclei were preserved. Even after this treatment the effect remained connected with the tissue fraction.

As a preparation to extraction with organic solvents the material was desiccated *in vacuo* from the frozen state. During this treatment the activity was destroyed completely.

Do virus and inhibitor combine in vitro?

Equal parts of immune brain suspension and FA virus were mixed = test solution *a*. A sample of the mixture was spun for 30 minutes in an angle centrifuge. The supernatant = test solution *b*. A control contained equal parts of FA virus and saline. The solutions, undiluted and diluted 1:100, were inoculated intracerebrally into 10 mice each. The result is tabulated in table V.

Table V.

Concentration	test *a*	test *b*	control
10^0	0.185	0.292	0.295
10^{-2}	0.094	0.152	0.157

Whereas there is a considerable reduction of the activity when the original mixture is inoculated, the virus in the supernatant is completely unimpaired. Hence, the virus is not destroyed nor does it combine with the inhibitor in vitro. At least, if a combination takes place, the virus must be very loosely attached, separable by means of low speed centrifugation. It is probable, therefore, that the mechanism of the effect is different from that of an ordinary virus-antibody reaction.

Development of tissue immunity during the course of infection.

25 mice were inoculated intracerebrally with the strain UIF. Groups of 5 mice were sacrificed 7, 14, and 21 days p.i. The remaining animals were tested for immunity after 28 days and, proving to be immune, sacrificed after a further 3 weeks. The brains in each group were pooled, prepared and tested as described above. The result is tabulated in table IV and depicted graphically in Fig. 3. The figures represent corrected y values.

Table VI.

Conc. of FA	1 week	2 weeks	3 weeks	7 weeks	control
10^{-2}	0.270	0.291	0.243	0.204	0.289
10^{-4}	0.182	0.233	0.163	0.122	0.175
10^{-6}	0.083	0.239	0.093	0.047	0.080

After 1 week the result does not differ significantly from the control. At this stage the brains contained only a small amount of UIF virus. After 2 weeks the virus content of the brains had reached its maximum. The preparation, however, does not afford protection against FA virus. On the contrary, addition of FA seems to induce in the UIF virus increased pathogenicity and encephalito-
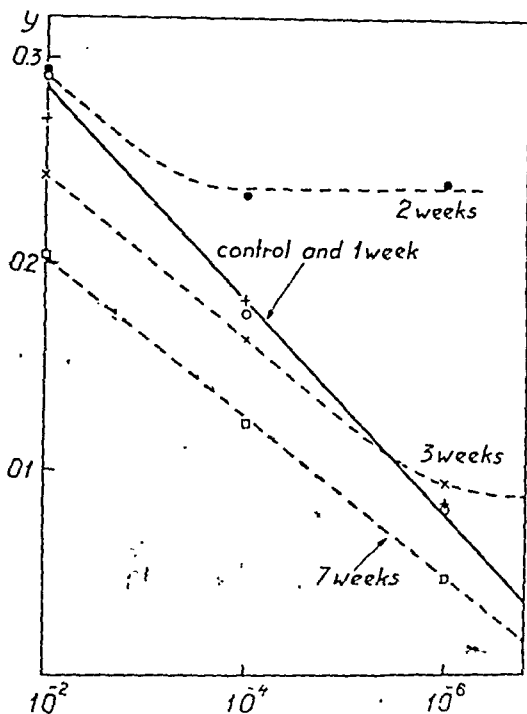
Fig. 3. Activity curves.
Full line: FA control. Dotted lines: FA + brain suspension.

genic properties. Thus, the effect is identical with the beforementioned influence on purified fecal virus. After 3 weeks a definite inhibitory effect is discernible. The course of the line of regression, however, tends to deviate in low concentrations of FA, although this may be a chance phenomenon (cf. page 44). After 7 weeks, finally, the protection is more pronounced and the line of regression has a normal rectilinear course. Thus, during the course of infection the appearance in the tissues of virus and of inhibitor do not coincide. In this particular case the virus preceded the inhibitor with about one week.

It was of considerable interest to correlate the appearance of inhibitor with the appearance of symptoms and of immunity demonstrable in vivo. A series of mice was infected with the UIF strain. One group was kept for recording of symptoms and incubation periods. Further groups of 20 animals were superinfected with FA virus at different times after inoculation. Animals contracting encephalitis were recorded as not immune. Finally, groups of 5 animals were used for the previous experiment. An
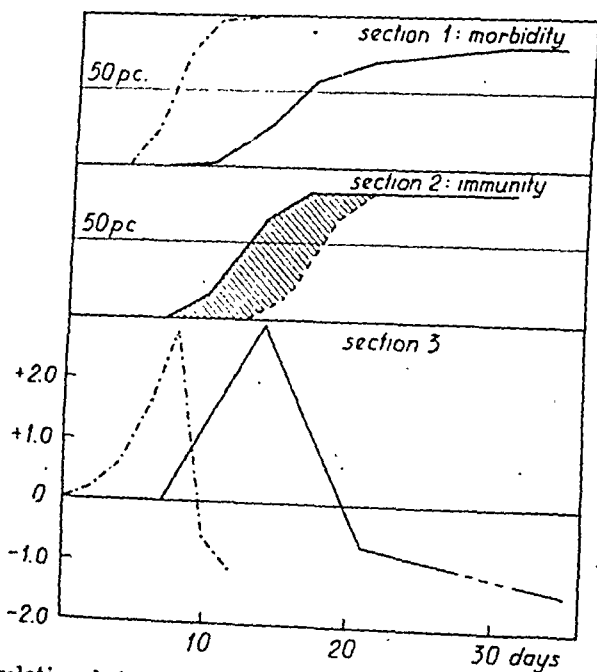
Fig. 4. Correlation between appearance o symptoms, immunity and inhibitor. Full line: strain UIF Broken line: strain UV. For further explanation see text

identical experiment was set up with the strain UV. In this case the in vivo test for immunity was valueless on account of the short incubation period and the high mortality rate characteristic of this strain. The results of these experiments are illustrated in Fig. 4.

Section 1 of Fig. 4, demonstrating the morbidity rate, needs no further explanation. Section 2 records the percentage of animals that were immune when tested with an intracerebral inoculation of FA virus at different times after the original infection. The full line refers to the dates of the test inoculation. When the incubation periods for the animals that proved not to be immune were calculated, the following average figures were obtained:

tested after	incubation period
10 days	5.6 days
14 »	4.8 »
17 »	4.5 »
21 »	4.0 »

Thus, the incubation period of the test infection decreases when the time passed from the original inoculation increases. When these incubation periods are added to the respective dates of the test inoculation, the dotted line is obtained. It must be assumed that some of the immune animals reached the state of complete immunity first some time after the test inoculation, i.e. that the actual course of the percentage immunity curve is to be found somewhere within the shaded area. With this in mind it is justifiable to conclude that the immunity demonstrable in vivo coincides with the appearance of symptoms.

Section 3 of the graph, depicting the development of inhibitor, is given with reservation for the difficulty to express the protection numerically. The zero line denotes the activity of the control; activation is recorded on the plus side, inhibition on the minus side. As the mechanism of activation seems to consist merely in an addition of a constant amount of virus, the degree of activation is recorded as the logarithm of the number of MID added. In order to obtain approximately comparable values of the inhibition the difference in y was calculated from the lines of regression in points corresponding to $y = 0.250$ of the control and these differences converted into log MID.

It is evident from Fig. 4 that there is a close coincidence in time between the appearances of symptoms, immunity and demonstrable tissue bound inhibitor. This holds true for both strains tested with their widely differing incubation periods.

Effect of intraperitoneal injection of inhibitor.

Groups of 20 mice each received a single intraperitoneal injection of 0.25 or 0.5 ml of an immune brain suspension. An intracerebral test inoculation of FA virus was given to different groups 24 hrs before, simultaneously with, 24 or 48 hrs after the treatment. An intracerebral test of the inhibitory effect was also included in the

experiment. The results are recorded in table VII. The figures are computed on the same basis as in Fig. 4, section 3.

Table VII.

Route	Amount	Treatment in relation to test inoculation			
		48 hrs before	24 hrs before	simultaneous	24 hrs after
i.c.	0.01			—2.40	
i.p.	0.25	—0.40	—0.57	—0.15	
	0.50		—1.35	—0.21	0.00

Intraperitoneal injection affords a definite protection but only when given simultaneously with or before the test inoculation. The material available does not permit any conclusions as to the duration of the protective effect but indicates that the optimal interval between treatment and inoculation is about 24 hours. The degree of protection is dependent upon the amount injected. It does not reach the level afforded by intracerebral injection and is, in relation to the quantity administered, of a quite different order of magnitude.

Discussion.

The basic phenomenon now described is essentially of the same type as that observed by Jungeblut and Sanders (11). As their latest article on this subject available to me appeared in August 1942 only the earlier part of their work can be dealt with in the following discussion.

In experiments with the highly virulent RMV and Aycock simian strains as test virus they found that intravenous injection of murine SK virus in the form of brain suspension in tissue culture fluid protected monkeys against the development of paralysis. The time relationships were as follows:

Treatment in relation to test	No. treated	No. protected	p.c.
2 weeks to 5 days before	14	3	21
24 hours before	12	10	83
simultaneous	38	24	63
3 days after	22	8	36
5 days after	6	0	0

As, generally, the test inoculations were not performed with graded amounts of virus, the percentage values in different experiments are not directly comparable but no doubt the figures quoted are tolerably representative of the protective effect exhibited. It may be said, therefore, that the results recorded in my table VII agree fairly well with Jungeblut and Sanders' monkey experiments. The pivotal point is that the effect obtained by extraneural injection does not last for any length of time. The maximum protection is afforded when the material is injected 24 hours before an intracerebral inoculation. Thus, active immunization as an essential feature of the mechanism of protection is out of question.

Jungeblut and Sanders attribute the protection to interference exhibited, directly or indirectly, by the active virus present in the brain suspension. They interpret the phenomenon as a domination of one virus over another. In their opinion this theory is supported by the fact that the effect is of a short duration. The SK murine virus, namely, is non-pathogenic and obviously non-infectious to monkeys. If injected, intra- or extraneurally alike, it is soon destroyed or excreted and, as a rule, its presence in the CNS cannot be demonstrated one week after injection. In their experiments the protective effect seems to be connected with the presence of murine active virus in the brain at the time of the test inoculation. In their opinion, therefore, the viral activity of the preparation must be of decisive importance. They write: »It may further be taken for granted that a definite correlation exists between the potency level of murine virus, as determined by titration in mice, and its interfering ability, as tested in monkeys.» This statement is obviously based on the fact that mouse brain suspension is superior to tissue culture virus and that cavian virus in the form of guinea pig brain suspension has given no unequivocal effects, the viral activity of the three materials decreasing in the same order as their protective power. However, unless experiments are carried out on one and the same material with varying viral activity, as in my table VI, there exists no evidence on which to base the above conclusion. On the other hand, the results are not incompatible with the idea that a tissue bound inhibitor is of primary importance for the establishment of the protective effect. In comparison to brain suspension the supernatant of tissue culture contains very little tissue. Hence, a specific tissue effect must be much less pronounced when tissue

culture virus is substituted for brain suspension. The failure of infected guinea pig or monkey brain to afford protection might be explained by fundamental differences in the mechanism of virus-host interaction in different host species.

I have had no opportunity so far to test the effect of my preparations in monkeys. Nevertheless, I feel convinced that there exists a far-reaching analogy between the phenomena described by Jungeblut and Sanders and by me. I cannot, however, share their views on the mechanism of the protective effect.

The experiments on mice described above seem to leave no doubt that the inhibitory activity is quite independent of the actual virus content of the preparations. Furthermore, they present suggestive evidence that the phenomenon of protection is connected with the presence of a specific inhibitor attached to the tissue. The final evidence, however, the complete separation of virus and inhibitor in different fractions of the same material, is not yet presented.

In my opinion, therefore, this phenomenon cannot be attributed to interference between two strains of virus. It is rather a demonstration *in vitro* of tissue immunity. In that case, however, the mechanism must be different from that observed in ordinary immunological reactions. The protective agent may be called an immune body but it is no antibody in the usual sense of the word. It does not combine with the virus *in vitro*. Neither are the quantitative relationships those of a neutralization reaction. Characteristic of the latter is the percentage law: in underneutralizing concentrations of antibody the ratio of free to neutralized virus is independent of the absolute quantity of virus present. In our case, on the other hand, the effect is more pronounced with large doses of test virus, not only absolutely but relatively. In Fig. 1, experiment 2, for instance, a given amount of inhibitor reduces the activity of 6,300 MID with 98.5 p.c. whereas, when the same amount of inhibitor is added to 6.3 MID, the reduction of activity is but 81.4 p.c. This phenomenon, unprecedented in immunology, seems to rule out a direct interaction between virus and inhibitor.

At present it is impossible to tell exactly where the point of attack is to be found. In all probability, however, it is located in the susceptible cell itself. The *modus operandi* might be a »blockade» of the cell or a change of the metabolism so as to restrict the repro-

duction of the virus. The following observation peviously described (14) seems to make the second alternative the more probable one. After intracerebral inoculation the FA virus is soon demonstrable in the spinal cord (24 hours p.i.), where a rise in titer is observed during the first days. At the onset of symptoms the concentration of virus in the cord is less than 1/10, usually about 1/100 of that of the brain. At this point further multiplication of the virus ceases in the cord as well as in the brain. The capacity of the spinal cord to maintain virus multiplication is not, however, limited to this level of potency, as shown in experiments using the intraspinal or intraperitoneal routes of inoculation. In these cases the virus content of the spinal cord attained the same maximum values as that of the brain after intracerebral inoculation. As shown in the present paper the appearance of inhibitor coincides with the onset of clinical manifestations of the disease. It is a plausible assumption that cessation of virus multiplication is caused by the action of the inhibitor produced. In that case a mere blockade of the cells already invaded by the virus would have no effect. It is most probable, therefore, that the inhibitor interferes in the mechanism of virus multiplication in the interior of the cell.

Another problem of major interest is concerned with the origin and the nature of the inhibitor. Is it a product of an altered cellular metabolism or does it originate in a transformation of the virus protein? This question might be intimately connected with a phenomenon illustrated in Fig. 3. Addition of FA to the 2 weeks' brain suspension induces in the myelitogenic strain enhanced virulence and encephalitogenic properties. In the 3 weeks' brain suspension, the viral activity of which as assayed by titration in mice is of the same order of magnitude, such induction if any (the slight deviation of the line of regression might very well be caused by chance) is only partial. It is possible, therefore, that the virus can appear in two different forms, for the present designated as free and bound virus. Free virus is inducible, bound virus is not. Whether this phenomenon has any connection with the degree of attachment of the virus to the tissue is not yet studied. It was observed, however, that about 10 p.c. of the total content of FA virus remained in the tissue debris, even after repeated washing with saline or distilled water. For the myelitogenic strains the corresponding figure was 50 p.c. or more. Additional trituration by grinding in the

colloid mill did not increase the yield of virus extractable. The fraction of the virus that can be extracted might behave as free, that attached to the tissue as bound. This attachment might be one link in the process of autosterilization, indicating a change in the chemical structure of the virus protein and eventually leading to complete loss of activity. Finally, it is possible that virus thus transformed might exact an inhibiting influence on the »normal» virus multiplication by diversion of the intracellular synthesis of virus protein or its basic constituents.

At the present stage of the investigation, however, these speculations may serve as a working hypothesis but nothing more. It is to be hoped that subsequent studies will produce more reliable evidence to this effect.

Summary.

Brain suspension from mice, surviving an attack of poliomyelitis induced by a strain of virus of low virulence and subsequently immune to reinfection, protects against infection when injected intracerebrally together with active virus. Normal brains do not posess this property.

The protective power is not dependent upon the virus content of the preparations and must, consequently, be attributed to the presence of a specific inhibitor. This inhibitor is attached to the tissue component of the suspension and is not soluble in distilled water or saline solutions. It does not combine with the virus *in vitro*.

The appearance of the inhibitor in the tissue coincides with the onset of symptoms.

A protective effect is obtained also after intraperitoneal administration of immune brain suspension, although less pronounced. The optimal effect is attained when treatment is given 24 hours before the test inoculation.

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Coexistence d'une leucémie lymphoïde et d'un carcinome.

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L'association d'une leucémie avérée et d'une tumeur maligne est un fait fort rare. P. Dustin (1), dans un travail récent ne retenait que quatre cas antérieurs au sien, où les deux affections étaient prouvées par biopsie, ou par autopsie. De même, l'un de nous a rencontré, dans les statistiques du Centre des Tumeurs de Bruxelles, un seul cas, où une leucémie lymphoïde est apparue chez un vieillard de 73 ans, traité antérieurement pour un épithélioma basocellulaire de l'oreille (2).

Le cas que nous rapportons ne se distingue en rien des cas antérieurs; il nous parait toutefois digne d'être rapporté, en raison de l'évolution du syndrome humoral, pendant que nous avons eu l'occasion de l'observer.

Observation:

Un homme de 59 ans, sans antécédents pathologiques notables, subit le 29 mars 1944 un traumatisme assez violent, qui détermine des contusions thoraciques. Employé dans une usine de vernis et peintures, il avait, un mois auparavant, consulté un autre médecin, en raison, vraisemblablement, du développement de son affection actuelle. A la suite de son traumatisme, un premier examen ne montre pas de lésions organiques (Dr. Godenne). Il apparait ensuite une bronchite (traumatique?), qui cède en huit jours au traitement appliqué. Cependant son état général ne s'améliore pas; il se plaint d'un affaiblissement rapide, sans autres malaises, sans douleurs. A noter, toutefois, que depuis quelques jours, il a de fréquentes épistaxis, et a eu une entéroragie.
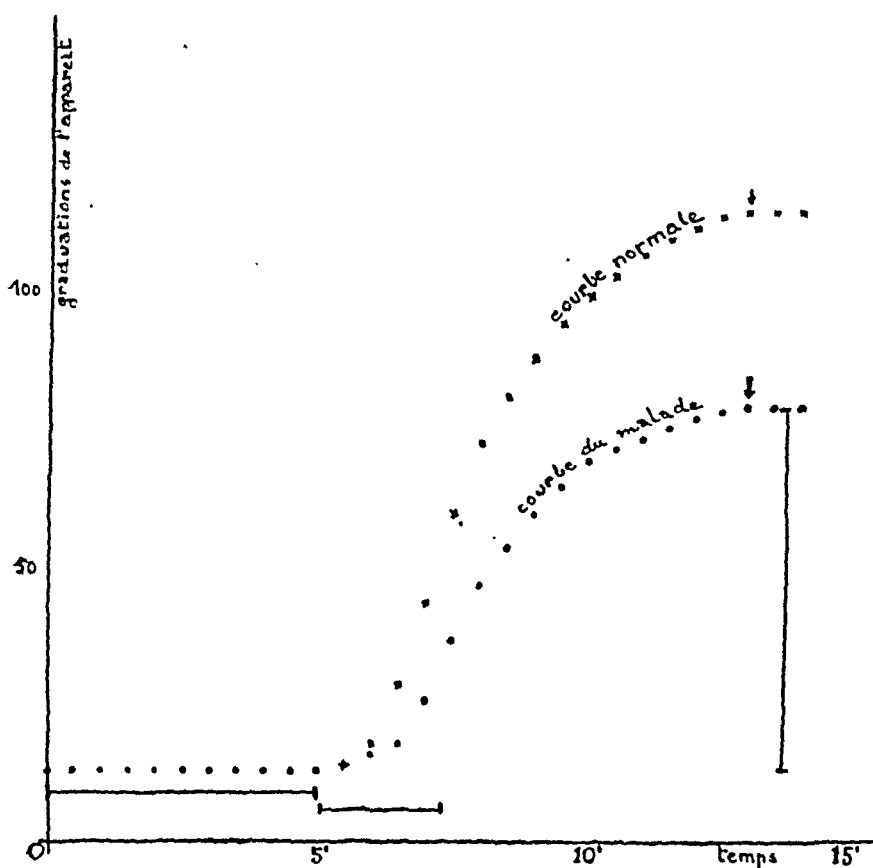
Figure 1: courbe photométrique de coagulation:
— phase de latence: durée normale (entre 5 & 7')
— angle de la courbe: = = 0.43 (augmenté par rapport à la normale — 0.1 à
  0 3 —) indique un déficit en vitamine K
— hauteur de la courbe: 67 graduations (diminué par rapport à la normale
  — au moins 100 —) indique une diminution du taux de fibrinogène.
— durée de la coagulation: normale (entre 10' et 15'). (pour la bibliographie,
  voir 10).

Si l'on reprend l'interrogatoire, système par système, on relève les
anomalies suivantes:
— dyspnée modérée
— saignements faciles et prolongés
— de petits signes gastriques (pesanteur postprandiale, avec vertiges)
— un méléna récent, très important.

A *l'examen physique*, on est frappé de prime abord, par le teint extrê-
mement pâle du malade, dont les téguments sont jaune cireux très pâle,
sans couperose, ni pétéchies. Il existe quelques gros rales humides dans les
deux champs pulmonaires, en arrière. On entend aux quatre orifices
cardiaques, un souffle systolique doux et musical, se propageant vers le

Figure II: frottis de rate, prélevé par ponction, 12 heures après la mort. L'étalement est constitué uniquement par des cellules allongées, pourvues d'un noyau assez volumineux, parfois nucléolé et d'un cytoplasme bleu clair, légèrement vacuolisé.

Van Wetter delevit

creux axillaire. A l'orifice mitral, le souffle est un peu plus rapeux. On entend de même un souffle le long des carotides, et un bruit de rouet caractéristique au niveau de la fourchette sternale. La tension artérielle est de 12.5/7.5 au Vaquez.

Le foie déborde le rebord costal de 5 cm. De consistance lisse, dur, non douloureux il paraît uniformément hypertrophié. La rate est légèrement augmentée de volume, elle mesure 15 cm à son grand axe, sa pointe est palpable en inspiration profonde. Elle est lisse et régulière. Il n y a rien d'autre à remarquer, si ce n'est la présence de quelques petits ganglions durs, isolés, indolores, roulant sous le doigt, situés dans les creux axillaires et inguinaux, et atteignant au maximum le volume d'un noyau de cerise.

En résumé, on retient une anémie extrême, avec cachexie à marche rapide, et l'on soupçonne le développement d'un cancer, particulièrement d'un cancer gastrique. C'est à ce moment, que l'un de nous pratique un examen hématologique (20/4/44), qui montre une leucémie lymphoïde chronique. Une radiographie gastrique, pratiquée à ce moment montre une image suspecte de néoplasie.

Evolution: on entreprend un traitement antianémique, auquel on adjoint quelques injections de vitamine K, indiqué par les anomalies de la courbe photométrique de coagulation, selon Meunier (voir figure I).

L'état général semble d'abord se stabiliser, les saignements diminuent. Le 25 avril, le malade se plaint de troubles de la sensibilité, dans les membres supérieurs; on refait l'examen neurologique, antérieurement normal, celui-ci montre une hypoesthésie diffuse des deux membres supérieurs, et surtout des retards de perception pour la thermo-algésie. A la suite, l'état général décline, sans que ces symptomes nerveux augmentent d'importance. Le 4 mai, nouvelle entérorragie importante. La cachexie progresse très rapidement et le malade décède le 9 mai. On trouvera dans le tableau suivant, l'évolution hématologique du cas. Il s'agit d'une leucémie lymphoïde des plus typiques.

Tableau des hémogrammes et des examens des centres hémopoï'etiques.

	15/4/44	20/4/44	6/5/44	Myelo-gramme	Autopsie
Globules rouges.........	1410000	1520000	1980000		
hémoglobine	36%	25%	26%		
leucocytes	40000	44000	32400		
plaquettes	—	23500	39000		
Neutrophiles	9%	2.66	14.8	7%	0.3
Eosinophiles		—	—	0.8	—
Basophiles		—	—	—	—
Métamyélocytes.........		—	—	1.4	0.1
Myélocytes		—	—	0.8	0.2
Promyélocytes		—	—	0.4	—
Lymphoblastes		2.66	4.4	1.0	0.8
Prolymphocytes		0.66	0.8	1.2	—
Lymphocytes	91%	83.0	75.2	79.0	97.8
Mitoses	—	0.33	—	—	—
Cellules de Rieder	—	—	2.4	—	—
Microlymphoblastes	—	—	1.2	—	—
Ombres de Gumprecht ..	—	4.0	—	—	—
Monocytes	—	0.33	0.8	0.4	—
Proérythroblastes	—	—	—	0.2	—
Erythroblastes basoph. ..	—	—	—	0.6	—
» polychroma.	—	—	—	1.6	—
» pycnotiques	—	—	—	5.0	0.5
Rapport G/R............	—	—	—	1.46	1.2
Plasmocytes	—	—	—	0.2	0.2
Cellules de Ferrata	—	—	—	0.4	—

Frottis de rate (prélevé par ponction 12 heures après la mort: 100 % de cellules mononuclées, pourvues d'un cytoplasme gris-bleuté, très allongé d'allure fibroblastique (figure II).

Frottis de foie (prélevé dans les mêmes conditions): montre les mêmes cellules mêlées à des cellules hépatiques et à de très rares polynucléaires.

Autopsie: cadavre amaigri, légèrement sub-ictérique. Petits ganglions axillaires.

Boîte cranienne: oedème méningé; dilatation moyenne des ventricules; pas de lésions vasculaires.

Cavité thoracique: coeur flasque, myocarde brunâtre; lésions végétantes d'endocardite au niveau des valvules aortiques. Pas d'autres lésions orificielles. Les deux poumons sont oedèmaciés. Scissurite moyenne droite.

Cavité abdominale:

Rate: mesure 13 × 10 × 4.5 cm. Consistance ferme; coloration de la capsule violacé; présence de trois infarctus récents sur la convexité. Pulpe homogène rouge, sombre.

Foie: très augmenté de volume: 24.5 × 20 × 10 cm. Farci de grosses nodosités d'aspect métastatique. Dessin lobulaire marqué. Vésicule applatie. Cholédoque dilaté (diamètre de petit. crayon).

Estomac, duodénum et anses intestinales: normaux.

Reins: légère sclérose.

Pancréas: normal.

Présence d'un volumineux ganglion métastatique préaortique. et de nombreux petits ganglions mésentériques en amande lisses et fermes.

Vessie dilatée, *prostate* légèrement augmentée de volume, molle.

Examens microscopiques.

1) *foie:* les travées hépatiques sont peu désorganisées; au niveau les espaces de Kiernan, on trouve de petits infiltrats lymphocyaires, parfois plus importants; c'est surtout au niveau des sinusoïdes, que l'on trouve de nombreux' lymphocytes épars. Les métastases sont constituées par un adéno-carcinome tubuleux, muco-sécrétant, riche en atypicités nucléaires, et ayant les caractères morphologiques des cancers des voies biliaires (figure III).

2) *rate:* les centres germinatifs des corpuscules de Malpighi ont disparu. La pulpe rouge est fortement modifiée par une hyper-plasie réticulaire, qui se retrouve après imprégnation argentique de la réticuline (technique de Foot, variante 1). Dans cette pulpe ainsi transformée, des infiltrats tantôt discrets, tantôt plus abondants, sont formés par de petits lymphocytes, qui parsissent plus indépendants les uns des autres que les lymphocytes normaux de la rate. Il existe de plus une importante sclérose périvasculaire, avec hyalinisation des tuniques artériolaires.

3) *ganglions mésentériques:* homogénéisation du tissu ganglionnaire; avec disparition du sinus périphérique et des follicules ger-
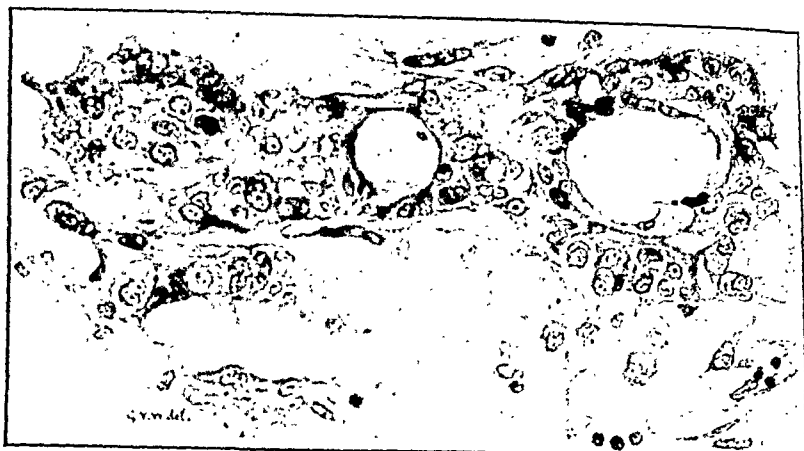
Figure III: métastase hépatique: adéno-carcinome tubuleux, avec légère muco-sécrétion, imbibant le stroma. Morrhologie rappelant celle des carcinomes des voies biliaires.

minatifs; les sinus sont étouffés et contiennent de nombreux lymphocytes, et quelques rares polynucléaires. La trame collagène est ténue, légèrement scléreuse.

4) *ganglion préaortique:* complètement envahi par un carcinome de même type que les métastases hépatiques.

5) *estomac (pylore):* la muqueuse n'est pas ulcérée, mais elle montre une très forte infiltration lymphocytaire, tantôt disséminée, tantôt disposée en amas sous-muqueux. Quelques traînées lymphocytaires, dans les espaces interstitiels de la musculeuse. Image lymphocytaire des contenus vasculaires.

6) *prostate:* aspect banal de cysto-adénome; une légère infiltration, purement lymphocytaire, se dessine, formant en de rares endroits des traînées et de petits nodules.

Conclusion: l'examen anatomique confirme l'existence de la leucémie lymphoïde; il permet d'exclure une lésion néoplasique de l'estomac, en ne montrant que de l'infiltration lymphoïde, à laquelle on peut, sans doute, rapporter l'image radiographique suspecte. Il existe cependant une néoplasie, ayant largement métastasié dans le foie, accompagnée d'une dilatation du canal cholédoque, avec vésicule, biliaire applatie, vraisemblablement cholédocienne, par conséquent.

Considérations générales.

Comme dans les observations connues, notre malade est assez âgé (en général, les autres cas furent observés entre 60 et 70 ans). Il en va de même, comme l'un de nous l'a montré, pour les cas de cancer doubles, soit successifs, soit simultanés, où les malades dépassent 50 ans, dans respectivement 84 % et 74 % (2).

1) *Au point de vue humoral*, quelques points de notre observation nous paraissent intéressants (tableau II):

Tableau des dosages effectués pendant l'évolution.

	20/4/44	6/5/44
Calcium inorganique	0.114 g. P.M.	
Phosphore inorganique	0.043 »	0.049 g. P.M.
Activité phosphatasique	10.3 u. Roberts %	16.5 u. Roberts %
Cholestérol total	0.742 g. P.M.	0.512 g. P.M.
Cholestérol estérifié	0.204 g. P.M.	0.249 g. »
Rapport estérifié/total	0.27	0.48
Glycémie....................	1.115 g. P.M.	»
Urée	0.55 g. P.M.	0.96 g. P.M.
Acide urique	0.032 g. P.M.	0.076 g. P.M.
Bilirubine totale	0.00571 gr. P.M.	0.01158 g. P.M.
Bilirubine directe	0.0	0.00894 g. P.M.
Bilirubine indirecte	0.00571 g. P.M.	0.00264 g. P.M.
Chlore sérique (en Cl)	—	3.29 g. P.M.

a) le taux des phosphatases alcalines du sang, évaluées en unités Roberts, passe, en quinze jours, de 10.3 à 16.5 unités %, alors que la calcémie était normale, lors du premier examen. On peut avancer deux hypothèses, pour expliquer ce fait; d'une part, il pourrait s'agir du développement de métastases osseuses, que, pour des raisons indépendantes de notre volonté, nous n'avons pu rechercher à l'autopsie; cependant, les métastases osseuses à point de départ biliaire sont rares; disons encore, qu'à aucun moment le malade ne s'est plaint de douleurs osseuses. D'autre part, nous sommes enclins à incriminer un début d'obstruction biliaire, qui s'accompagne effectivement d'une forte élévation du taux des phosphatases alcalines du sang (Deloyers, 3). La coexistence d'une cholestérinémie progressivement abaissée est à rapprocher des

constatations de Schiffman et Winkelman après ligature du cholédoque chez le chien (ibidem, page 395).

b) ce début d'obstruction biliaire, observé, on s'en souvient, à l'autopsie, est également responsable de la modification de la formule bilirubinémique de notre malade; en effet, sa bilirubine, entièrement indirecte, à 5 mg pour mille, le 20/4/1944, passe à 11.5 mg pour mille, quinze jours plus tard, dont 8.1 mg de bilirubine directe. Nous rapporterons encore à cette lésion, l'insuffisance en vitamine K, décelée photométriquement.

c) l'augmentation brusque du taux d'urée (0.55 à 0.96 gramme pour mille) doit surtout être mise sur le compte de la résorption de sang, à la suite de la dernière entéroragie; on retrouve, en effet, ce signe toutes les fois que du sang est résorbé dans l'organisme (hémorragies graves postopératoires-Blankoff et Delcourt-pneumonies-Peromet, (4)); il s'y ajoute peut-être une légère insuffisance rénale, étant donné le léger abaissement du taux des chlorures sériques, et la sclérose rénale constatée à l'autopsie.

d) signalons, enfin, l'abaissement extrême et progressif du taux de cholestérol, avec cependant une amélioration du rapport cholestérol estérifié/cholestérol total, peut-être sous l'influence du traitement hépatothérapique.

2) *Au point de vue hématologique:*

a) il s'agit bien d'une leucémie lymphoïde, et non d'une réaction lymphatique leucémoïde, telle qu'on en a rarement signalée, au cours des cancers (Bichen, Reich, Silberstein et Pechterewa). La formule sanguine, avec sa légère poussée lymphoblastique terminale, la formule du myélogramme, avant et après la mort, la transformation leucémique de la rate et des ganglions, enfin, sont autant d'arguments en faveur de la leucémie.

b) nous insisterons particulièrement sur la morphologie des étalements des ponctions spléniques et hépatiques, pratiquées, il est vrai, douze heures après la mort. Dans la rate, l'uniformité de l'étalement est caractéristique; il s'agit de cellules dont le caractère nucléaire les apparente aux jeunes lymphocytes, mais qui possèdent un protoplasme étiré, d'allure fibroblastique. Leur aspect est assez proches de certaines images de sarcomatoses ganglionnaires montrées par Tischendorf. Il ne s'agit pas de cellules altérées

ponctionnées au niveau des infarctus, puisqu'on les retrouve identiques et mêlées à des cellules hépatiques, dans l'hépato-gramme. Nous interprétons ces images comme étant un nouvel exemple de la parenté qui existe entre certains lymphosarcomes et les lymphadénoses.

c) l'examen de la moelle n'a pu nous montrer si des métastases néoplasiques avaient envahi le squelette, à cause de l'étouffe-ment des autres lignées par les cellules mononucléées. La répartition des cellules granuleuses, celle des érythroblastes et le rapport granulocytes/érythroblastes sont analogues à ce que l'on trouve dans les leucémies lymphoïdes simples (voir de Weerdt, 5).

d) notons, enfin, à la suite de Dustin, que l'évolution de la leucémie n'a été en rien modifiée par la présence d'une néoplasie. On peut seulement affirmer que cette association morbide a con-courru à accélérer la fin du malade.

3) *Au point de vue anatomo-pathologique:*

a) la coexistence d'un cancer et d'une leucémie lymphoïde est une pure coincidence; la nature et la situation du cancer, pas plus que son pouvoir plus ou moins métastasiant n'ont d'importance; parfois même, le cancer apparaît chez un malade déjà leucémique an-térieurement (Scheuffler).

b) bien que nous n'ayons pu le démontrer morphologiquement, nous suspectons la possibilité de métastases osseuses chez notre malade. C'est une éventualité rare, puisque Geschickter et Cope-land n'en signalent que 3 cas, sur 334 cas de métastases osseuses d'origine diverses, soit environ 1 % (6).

c) nous n'avons pas été aussi heureux dans nos investigations que Dustin, qui a pu saisir le mode d'invasion des cellules carcinoma-teuses, dans un ganglion leucémique. Le seul ganglion métastati-que que nous avons observé était entièrement envahi par la tumeur, et il ne subsistait pas de tissu lymphoïde. Mais les images que nous avons observées dans le foie semblent montrer que chaque proces-sus évolue pour son propre compte, sans influencer l'autre. Il n'est pas possible d'affirmer la précession de l'un d'eux.

Résumé.

Etude biochimique, hématologique et anatomo-pathologique d'un cas de coexistence de leucémie lymphoïde avec un carcinome, vraisemblablement issu des voies biliaires. On retient particulièrement l'évolution du taux des phosphatases alcalines du sang et de la bilirubinémie, sous la dépendance d'un début d'obstruction des voies biliaires. Les deux affections paraissent évoluer indépendamment l'une de l'autre.

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The importance of adequately recorded results in the Rehberg kidney test.

By

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Both renal activity as a whole as well as its principal partial processes are of a highly complex nature; the component factors are numerous and of many kinds, and they are closely interwoven with each other in multifarous ways. Care and caution are necessary in drawing conclusions from experiments where the fluids formed are studied in the places where they are being elaborated. Interpretation of the balance of factors involved becomes still more difficult when conclusions are drawn on the basis of blood- and urine-analyses, as in the renal clearance tests used in experimental and clinical research. Inadequate experiments and conclusions are so commonly found in the literature on the kidney that an account of the principles involved and a criticism of some major mistakes found in the current literature would seem to be of interest, not to say urgently required.

Such an account will be given below. The remarks submitted render it very evident, that even modern renal literature displays a very imperfect appreciation both of the really important points of filtrative-reabsorptive renal function as well as of the real implications of several of the principal methods commonly used for exploring the activities of the kidney. The same conclusion is also obvi-

ous both from my earlier paper in this journal (Ekehorn: Inulin as a substitute for creatinine in renal tests. Acta med. Scand. vol. CXVIII, 1944, p. 114) as well as from my second renal monograph (Integrative Natur der normalen Harnbildung), where the literature up to 1937—38 is discussed extensively.

Renal function is the sum of glomerular and tubular prestanda.

As I mentioned above, the renal clearance tests with creatinine or inulin do not appear to be much understood by the majority of renal workers. Although these tests are commonly used all over the world in physiological and clinical kidney research, yet they are almost universally performed in a most defective manner. These tests are able to give detailed quantitative data not only of the glomerular but also of the tubular prestanda. Both these functions are necessary for the formation of urine, but the latter is clearly the more important function. Nevertheless, the information concerning the tubular prestanda, so easily obtained from these tests, is practically never duly considered by renal authors and is often disregarded altogether. This is so grave a misapplication of these tests and is such an unsatisfactory way of exploring kidney function as to be compatible only with for instance examination of the heart by means of electrocardiograms, from which all particulars except the auricular parts have been erased. Electrocardiograms showing nothing more than the P-waves are clearly of hardly any use. Similarly defective methods of analysis are no better in the case of the kidney: The glomerules perform like the auricles only preliminary, although necessary, functions, whereas the tubules like the ventricules are charged with the main burden of the total function of the resp. organ.

The minute-volume of the glomerular filtrate, *i.e.* the creatinine — (or inulin-)clearance, having been determined by means of these tests, the filtered minute-amounts of every urinary constituent are easy to compute, as they equal the product of the filtrate-volume per minute and the constituent's plasma-concentration. By comparing these filtered amounts with the amount of the same substance contained in the simultaneously formed bladder urine, we obtain information of how much the tubules have (secreted or) reabsorbed of the substance. All that is required for computing these important data is to determine *i*) creatinine-clearance $\dfrac{U \cdot C_u}{C_b}$ (crea-

tinine conc. of blood and urine C_b & C_u, and the minute-volume of the latter, U) *and ii*) the blood and urine concentrations of the urinary solute, the excretion of which one desires to study. If only renal water-excretion is involved the task of computing the tubularly reabsorbed quantities is still simpler and consists merely in subtracting U from creatinine-clearance.

The utter simplicity of computing the amounts of water and urinary solutes, reabsorbed by the tubules, renders it altogether inexplicable, why authors *almost universally neglect doing so*, and why the vast majority of authors *even neglect to report their experiments so completely that others may recalculate the neglected resorptive data from their records.* Considering that the tubularly resorbed quantities with but a few exceptions never have been properly computed, it is clear that opinions regarding tubular resorption generally remain utterly confused, fragmentary, and conjectural; they are often altogether erroneous.

This neglect of the quantitative data for tubular function appears still stranger, if we consider that *the tubules universally are credited with the whole task of transforming the glomerular filtrate* (that merely is plasma deproteinized) *into urine,* which implies *a very great number of important qualitative as well as quantitative changes of the original filtrate fluid.* Nobody disputes nowadays that glomerular fluid is an ultrafiltrate from the plasma, and that its volume greatly exceeds the volume of the final urine. Consequently the entire task of reabsorbing the excess water and of effecting the whole chemical transformation of the filtrate into urine falls to the tubules. This chemical transformation is in any case mediated by the tubuli, whether the tubules effect it solely be reabsorption of water and solutes from the filtrate or whether they also secrete some solutes into it, as has been suggested by some authors.[1]

Creatinine-tests are as suitable for determining the amount of tubularly secreted substances (if any such existed among the

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[1] There are several versions of this view, all most unwarranted. The last one, which has been propagated with much force, contends that up to 25—40 % of the urinary creatinine may be secreted by the tubules of man and anthropoid apes, whereas the remainder is filtered in the glomeruli. Water and all other natural-urinary constituents during health and disease, however, are reabsorbed by the tubules in varying degrees according to this view, because they have lower clearances than creatinine and inulin. This view of partial tubular secretion of creatinine in man and apes has been considered by me in my preceding paper in this journal and found untenable.

natural plasma-preformed constituents of the urine) as for deter-
mining the amounts of urinary constituents filtered in the glomeruli
or resorbed by the tubules.   Why should appropriate considera-
tion of the easily calculable tubular data then be almost universally
neglected in creatinine (and inulin) tests?   Why studiously avoid
to collect all the easily obtainable information concerning a most
essential renal function, which properly treated Rehbergian tests
are able to give?   Why disregard the axiom, that the whole urine,
U, as well as the amounts of water and of every urinary solid and all
variations therein, is the sum of, or the difference between,
glomerular action G and tubular action T?   Why this total
disregard of the second factor of the equation

$$G \pm T = U?$$

The scarcity of tubular data in renal papers.

*This strange reluctance against comparing filtrative with reab-
sorptive data, and,* indeed, *against merely computing the latter pro-
perly,* is amply borne out by the very large material comprised in
my book »Integrative Natur der normalen Harnbildung» (cf. dis-
cussion and further references loc.cit. p. 1155—57).

Thus one author has performed about 530 Rehberg's creatinine tests,
inclusive of over 200 tests on persons with healthy or practically
healthy kidneys; the tests have been executed with a rare degree of tech-
nical care and skill. Yet the author *constantly fails to compute or note the
tubularly reabsorbed quantities of water.* This omission is easily made good,
as the author has always reported the minute-volumes of the urine in his
tables, so the reader has just to subtract this from the tabulated filtrate-
volumes per minute.

This omission, however, has prevented the original author from observ-
ing the abundant information his own material provides as to several
important items of the regulation of urinary water excretion. *These ques-
tions are not mentioned with one word in the original paper,* the main theme of
which is the renal excretion of *uric acid.* Nor are the filtered and reabsorb-
ed quantities of uric acid computed, and still less compared. Nevertheless,
the observations made are in every instance sufficient for such computa-
tion: the filtered amounts of uric acid are the product of the filtrate-
volume and the uric acid concentration of plasma, which both are con-
sistently reported; so is also the amount of uric acid in the final urine.
The difference between these amounts is, of course, the tubularly reab-
sorbed uric acid. It is, no doubt, a strange way of studying renal excre-

tion of uric acid, when one i) collects all the data required for computing quantitatively both the glomerular and the tubular prestanda in respect of this substance, and ii) then consistently neglects to perform this calculation in spite of the obvious fact, that these two prestanda together constitute renal excretion of uric acid. In spite of its excellent and singularly complete material, the original paper is therefore rather inclusive; its analytical discussion of the collected data is confined to comparisons between i) the concentration indices [1] of creatinine and uric acid, and ii) between the minute-volume of the glomerular-filtrate and the absolute amount of uric acid in the urine per minute. What can be obtained from such comparisons, when neither of the two factors primarily responsible for uric acid excretion is determined at all and still less properly considered?

Another author, whose investigations as a matter of fact also contain very much valuable information, is extensively dealt with in the »Integrative Natur der normalen Harnbildung» (cf. ref. on preceding page). He has performed over 100 Rehbergian tests, but has *in no instance computed the tubularly reabsorbed amounts*, not even in the case of water, where this computation merely consists in subtracting the minute-volumes of the urine from the creatinine-clearances determined, and where determination of the latter in any case presupposes measurement of the urinary volume. *Not only are the tubularly reabsorbed amounts* never computed, the computation *of the filtered quantities of the various urinary substances* is also neglected, excepting, of course, the water, the filtered amount of which happens to be the same as creatinine clearance.

The study of a complicated and variable composite function like kidney activity implies with necessity determination of at least its primary component processes, glomerular and tubular action, the algebraic sum of which do constitute kidney function in respect of every urinary constituent. Almost universal and complete neglect of the one and more or less inadequate consideration of the other primary component prevents authors from extracting more than a fraction of the information that may be contained in their own experimental material. Such neglect, further, may easily bring about, that much valuable information is lost altogether to renal science.

A third paper was discussed in some detail in the »Integrative Natur der normalen Harnbildung» (p. 448—56). Although the author specially *wants to examine renal water excretion* and the mechanism for increasing and restricting urinary water output, yet *he constantly forgets to compute the tubularly reabsorbed quantities of water* although it just remained to sub-

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[1] Conc. index is the quotient $\frac{Cu}{Cb}$ where Cu and Cb are the urine and blood concentrations of the substance in question.

Table

Urine sample	Creatinin, mg per 100 cm³ in		Creatinin concentrat. index $\frac{Cru\ \%}{Crp\ \%}$	Amount of urine cm³/minute	Amount of filtrate cm³/minute = $C \times U$	Amount of fluid resorbed cm³/minute = $F-U$	Urea, mg per 100 cm³, in		Urea filtered mg/min.= $= F \times \frac{Up\ \%}{100}$
	urine	plasma	C	U	F	R	urine	plasma	
	Cru %	Crp %	C	U	F	R	Uu %	Up %	Fu
1......	515	7.75	66.5	2.03	135	133	2,103	54.60	73.60
2......	582	7.10	82	1.51	126	124.5	2,460	50.50	63.60
3......	861	6.70	129	1.11	143	141.9	3,025	47.25	67.5
4......	426	6.30	67.6	1.74	118	116.3	2,300	44.30	52.10
5......	97	5.50	17.6	6.75	119	112.3	646	42.80	51.0
6......	40	4.85	8.25	15.22	126	110.8	295	41.60	52.2
7......	35	4.60	7.6	19.25	146	126.8	256	41.0	60.0
8.....	68	4.35	15.6	7.16	112	104.0	475	40.0	44.8
9......	177	3.90	45.3	1.26	57	55.8	1,250	39.60	22.6
1.....	1,258	8.65	145	0.67	97	96.3	1,392	16.90	16.4
2......	1,261	7.70	164	0.70	115	114.3	1,436	17.10	19.7
3.....	1,111	6.20	179	0.78	140	139.2	1,522	18.0	25.2
4......	1,223	5.20	236	0.54	127	126.4	1,840	17.35	22.05
5.....	1,096	4.50	244	0.51	124	123.5	1,890	16.70	20.65
6.....	1,129	3.85	293	0.44	129	128.6	2,080	17.35	22.4
	I	II	III	IV	V	VI	VII	VIII	IX

1st exper. 5 g Creatinine + 200 cm³ water per mouth at 9.30; 20 g urea + 11.06; 1st urine 11.42, 73 cm³; 12.05 2nd bloodsample; 12.10 2nd urine por- 200 cm³ water & 3rd blood sample; 1.37 urine 68 cm³; 2.05 urine 189 cm³; 3.18 5:th Bloodsample; 3.33 urine 279 cm; 3.57 urine 49 cm³; 4.15 6th blood-

2nd exper. 5 g Creatinine + 200 cm³ water per mouth at 10.19; 10.57 1st pletely). 11.48 2nd bloodsample; 12.10 —12.30 lunch + 300 cm³ water, etc. 5

tract the carefully recorded urine volumes from the simultaneous filtrate-volumes. This omission is the more surprising, as the author already at the outset of his paper believes himself to have found strong reasons for attributing the regulation of renal water excretion to variations of tubular water reabsorption. Determination of the amounts of tubularly reabsorb-ed water and study of the manner and degree of the possible variations of these amounts would otherwise appear to be the primary object for an investigation aiming at crediting the tubules with the task of regulating urinary water output. The neglect of this more than obvious procedure in every one of the 50 creatinine-tests performed is also responsible for the

rea excreted mg/min. = $U \times \dfrac{Uu\%}{100}$	Urea resorbed mg/min. = $= Fu - Uu$	Urea in the reabsorbed fluid, mg pr 100 cc = $\dfrac{Ru}{R} \times 100$	Percent of filtered urea which is excreted = $\dfrac{Uu}{Fu} \times 100$	Percent of filtered urea which is resorbed	Concentrat. ratio of urea = $\dfrac{Uu\%}{Up\%}$	Urine sample	Time
Uu	Ru	Ur %	Eu %	$100 - Eu\%$	Cu		
42.75	30.85	23.2	58	42	38.6	1	11.06 -11.12
37.9	25.7	20.6	59	41	48.7	2	11.12- 12.10
33.6	33.9	23.9	50	50	61	3	12.10 -12.58
40.0	12.1	10.4	77	23	52	4	12.58- 1.37
43.6	7.4	6.6	85	15	15.1	5	1.37 - 2.05
45.0	7.2	6.5	86	14	7.1	6	2.05- 2.27
49.30	10.7	8.45	82	18	6.25	7	2.27 - 2.51
34.0	10.8	10.3	76	24	11.9	8	2.51- 3.33
15.75	6.85	12.3	70	30	31.6	9	3.33 - 3.57
9.33	7.07	7.35	57	43	82	1	11.07 - 11.54
10.06	9.64	8.44	51	49	84	2	11.54 -12.50
11.9	13.3	9.55	47	53	85	3	12.50- 1.57
9.95	12.10	9.55	45	55	106	4	1.57- 2.19
9.65	11.0	8.9	46.5	53.5	113	5	2.19 - 3.36
9.16	13.24	10.3	41	59	120	6	3.36 - 4.26
X	XI	XII	XIII	XIV	XV		

200 cm³ water per mouth at 10.10; 1st bloodsample 11.02; Bladder emptied tion 43 cm²; 12.15—12.40 Lunch + 400 cm³ water; 12.58 urine 53.5 cm²; 1.09 2.15 400 cm³ water & 4th bloodsample; 2.27 urine 335 cm³ 2.51 urine 520 cm²; sample.

bloodsample; 11.07—11.54 1st urine portion (bladder first emptied com- further bloodsamples at 12.40, 1.45, 2.37, 3.27, 4.17.

fact that most of the authors conclusions, arguments, and curves are inva- lid throughout; indeed, they are directly negatived by his own material, as soon as his omission to determine the reabsorbed water amounts is made good.

Among the over 700 creatinine-tests from the earlier literature that have been discussed in »Integrative Natur der normalen Harnbildung» only four series of together 35 tests, i.e. less than 5 %, bring out the resorptive data, which otherwise are neither

Table

Urine sample	Creatinine, mg per 100 cm³, in		Creatinine Concentration index	Amount of urine cm³ per min.	Amount of filtrate, cm³ per min.	Amount of fluid resorbed, cm³ per min.	Chlorine, mg per 100 cm²	
	urine	plasma					urine	plasma
1	907.0	8.05	113.0	1.77	200	198.2	428.0	371.5
2	992.0	7.40	134.0	0.96	128	127.0	594.0	372.6
3	1,161.0	5.90	197.0	0.71	139	138.3	668.0	370.
4	225.0	5.45	41.0	2.90	119	116.1	185.6	366.
5	68.5	5.80	11.8	12.20	144	131.8	44.4	364
6	44.8	6.00	7.5	17.60	132	114.4	34.8	362
7	39.4	5.70	7.6	17.30	131	113.7	32.1	362
8	42.1	5.25	8.0	14.95	120	105.0	27.5	36
9	38.4	4.55	8.4	14.70	124	109.0	23.6	36
10	44.4	3.95	11.2	9.95	112	102.0	22.5	36
11	48.0	3.83	12.5	10.50	132	121.5	22.1	36
12	54.4	3.83	14.1	8.70	123	114.3	27.2	36
1	933	6.65	140	0.92	129	128.1	920	3?
2	546	5.60	98	1.29	126	124.7	1.028	3?
3	302	5.05	60	2.18	130	127.8	1.061	3?
4	144	4.75	30	4.58	139	134.4	878	3
5	244	4.45	55	2.23	122	119.8	1.003	390.0
6	267	4.05	66	1.65	109	107.35	1.007	388.5
7	252	3.85	65.5	1.70	111	109.3	1.034	383.0
8	264	3.77	70	1.59	111	109.4	1.028	381.75
	I	II	III	IV	V	VI	VII	VIII

1st Experiment: 5 g Creatinine at 9.27; 10.38 1st bloodsample; 10.44 lit. water 12.50—2.17. Further bloodsamples at 1.03, 2.03, 3.33 & 4.33.

2nd Experiment: 5 g Creatinine at 9.19; 10 g NaCl at 9.53; 10.55. Bladder sample; 12.50 3d bloodsample; 12.55—1.10 Lunch; 1.10 600 cm³ water. Further

reported, computed, nor considered in the remaining 95 % of the tests (530 + 104 + 50 tests).

This large majority of tests represent no doubt a very inappropriate and superficial manner of analyzing filtrative-reabsorptive renal processes when we consider that we possess an experimental method suitable for detailed differentiation between and for quantitative measurement of the principal partial processes of the kidney.

Chlorine filtered mg per min.	Chlorine excreted mg per min.	Chlorine resorbed mg per min.	Chlorine in the reabsorbed fluid, mg per 100 cm³	Per cent of filtered chlorine, which is		Time
				excreted	resorbed	
741	7.58	733.4	371.0	1	99	10.44—11.15
499	6.68	492.3	369.9	1.3	98.7	11.15—12.01
514.5	4.72	509.8	368.5	0.9	99.1	12.01— 1.09
438	5.36	432.6	371.0	1.2	98.8	1.09— 1.36
526.5	5.43	520.1	394.1	1.0	99	1.36—1.54
476.5	6.14	470.4	411.7	1.3	98.7	1.54— 2.10
475	5.56	469.4	412.9	1.2	98.8	2.10— 2.27
435	4.12	430.9	411.5	0.9	99.1	2.27— 2.49
455	3.48	451.5	411.5	0.8	99.2	2.49— 3.22
411	2.24	408.8	401.0	0.5	99.5	3.22— 3.58
486	2.32	483.7	398.7	0.5	99.5	3.58— 4.21
464	2.37	461.6	395.3	0.5	99.5	4.21— 4.42
498	8.43	489.6	384.5	1.7	98.3	11.01— 11.49
499	13.3	485.7	389.5	2.7	97.3	11.49—12.32
520	23.2	496.8	387.3	4.5	95.5	12.32— 1.16
553	40.2	512.8	381.65	7.3	92.7	1.16— 1.53
484	22.4	461.6	384.8	4.6	95.4	1.53— 2.41
423	16.6	406.4	379.5	3.9	96.1	2.41— 3.33
427	17.6	409.4	372.9	4.1	95.9	3.33— 4.0
423	16.3	406.7	372.4	3.9	96.1	4.0 — 4.41
IX	X	XI	XII	XIII	XIV	

bladder completely emptied. 11.30 2nd bloodsample; 12.30—50 Lunch. 3

completely emptied & 1st bloodsample; 11.13 10 g NaCl; 11.54 2nd blood-
bloodsamples at 2.25, 3.40 & 4.35.

It is worth remembering, however, that *the real proportion of adequately performed creatinine-tests is very much lower than corresponds to the figures 35: 700 or the rate 5: 95.* As a matter of fact, it has practically always been possible to supplement the original omissions more or less completely in the above-mentioned series of 684 defective creatinine-tests. Indeed, these tests have for this very reason been selected for discussion in the »Intregrative Natur der normalen Harnbildung» out of a vast majority of tests,
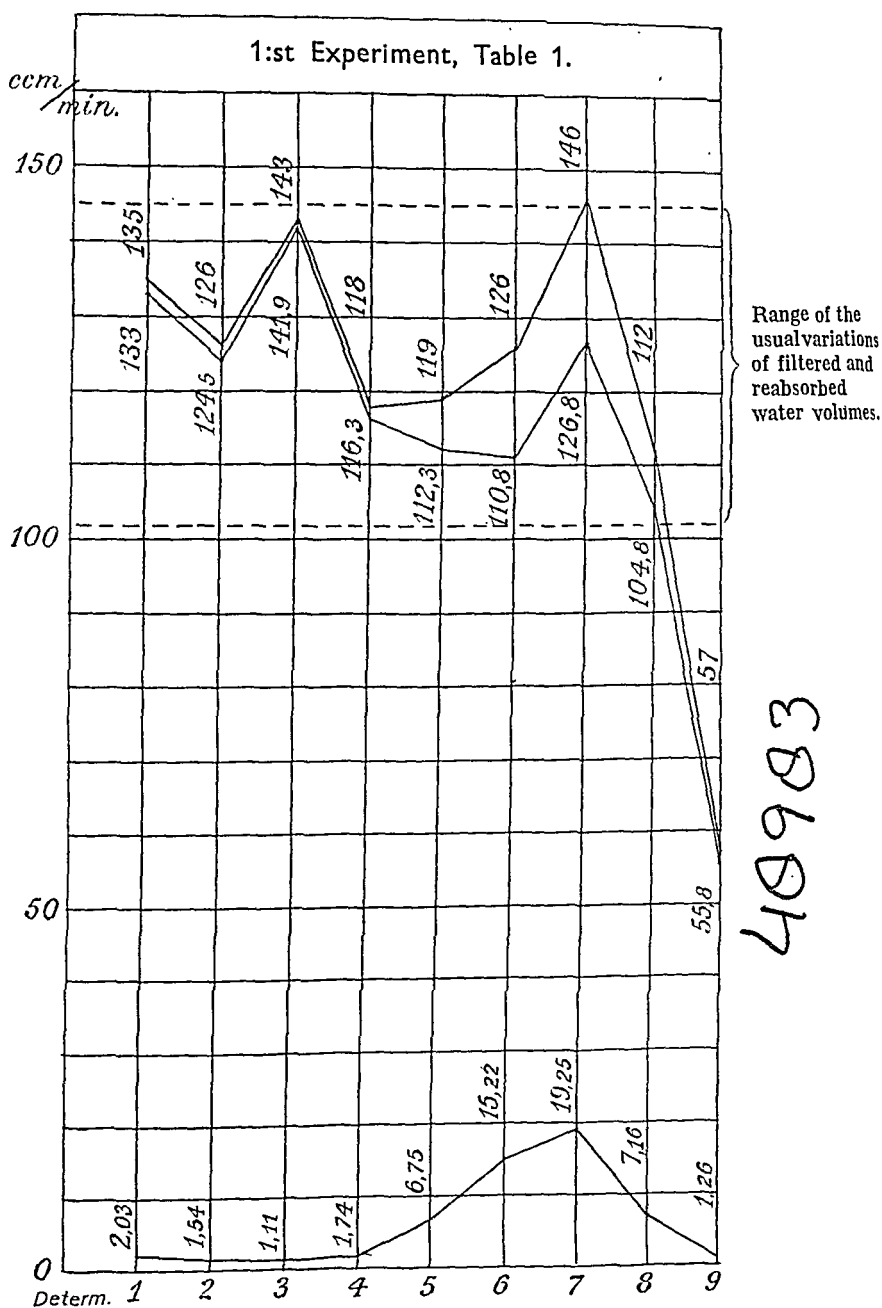
Fig. 1. From above downwards: Curves of filtered, reabsorbed, and excreted water in cm³ per minute.

Water.
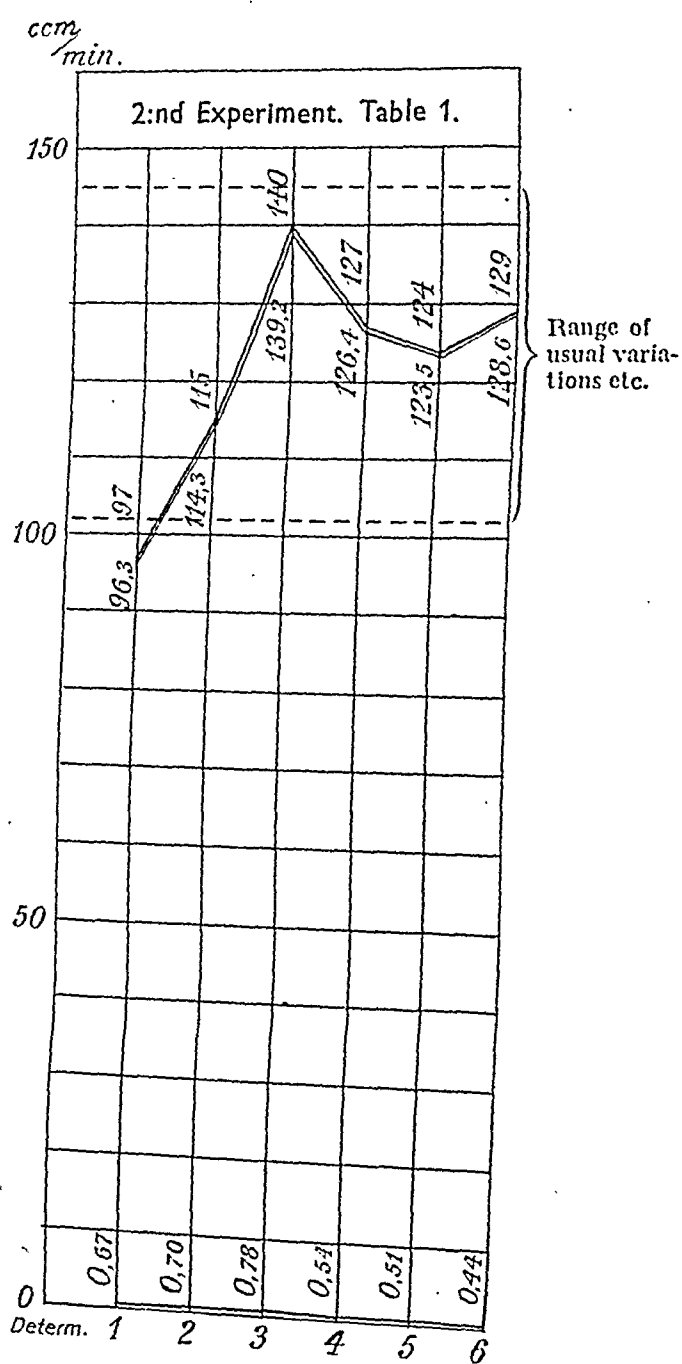
Fig. 2.   Curves and units as in Fig. 1.
Water.
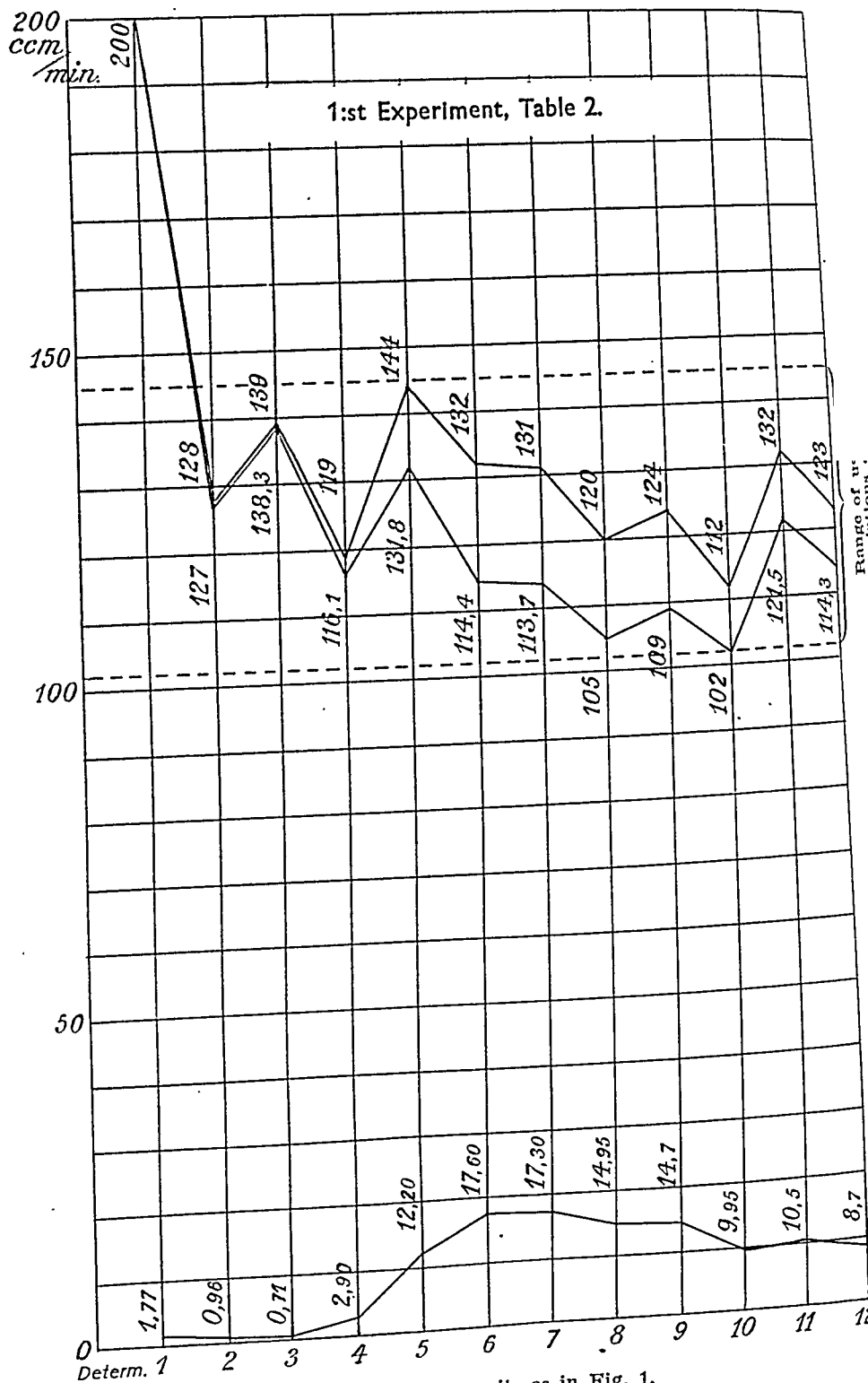
Fig. 3. Curves and units as in Fig. 1.
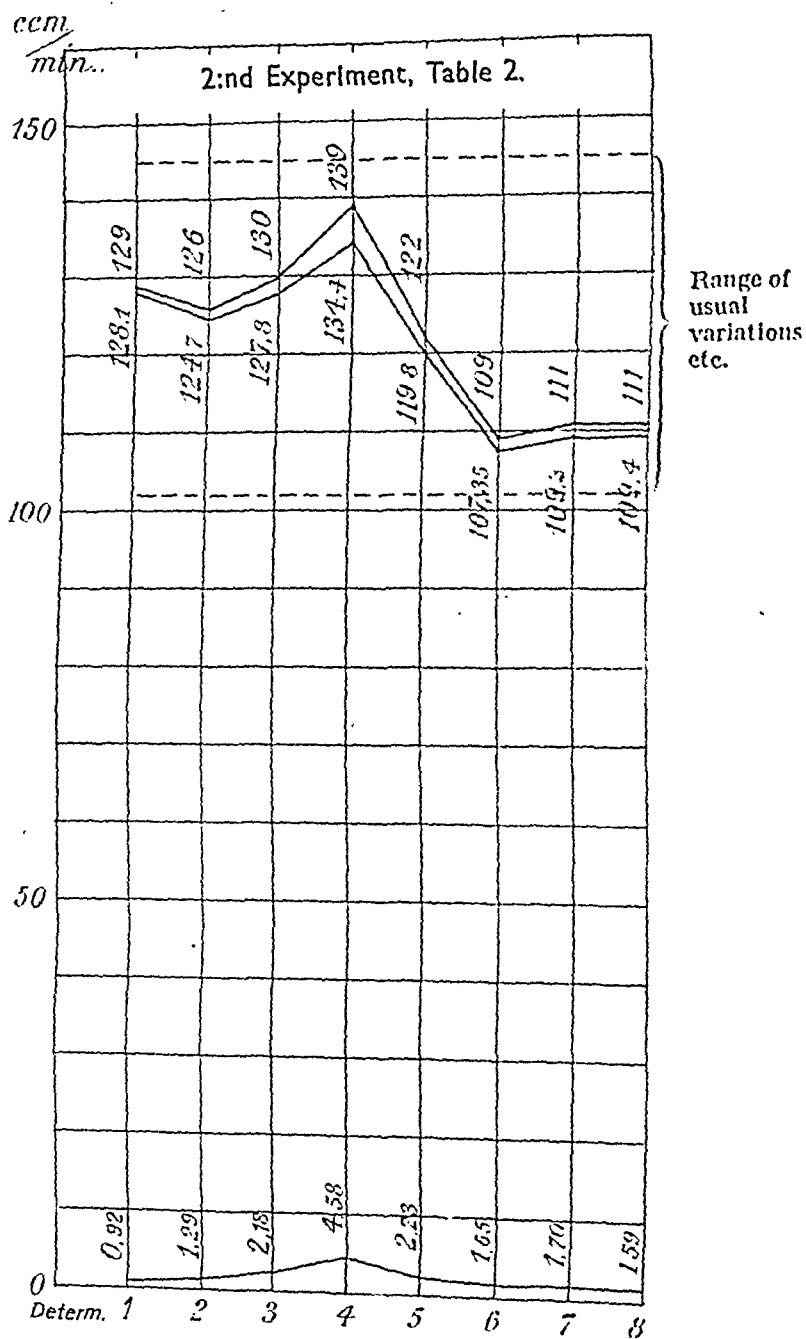
Water.

Fig. 4.   Curves and units as in Fig. 1.

Water.
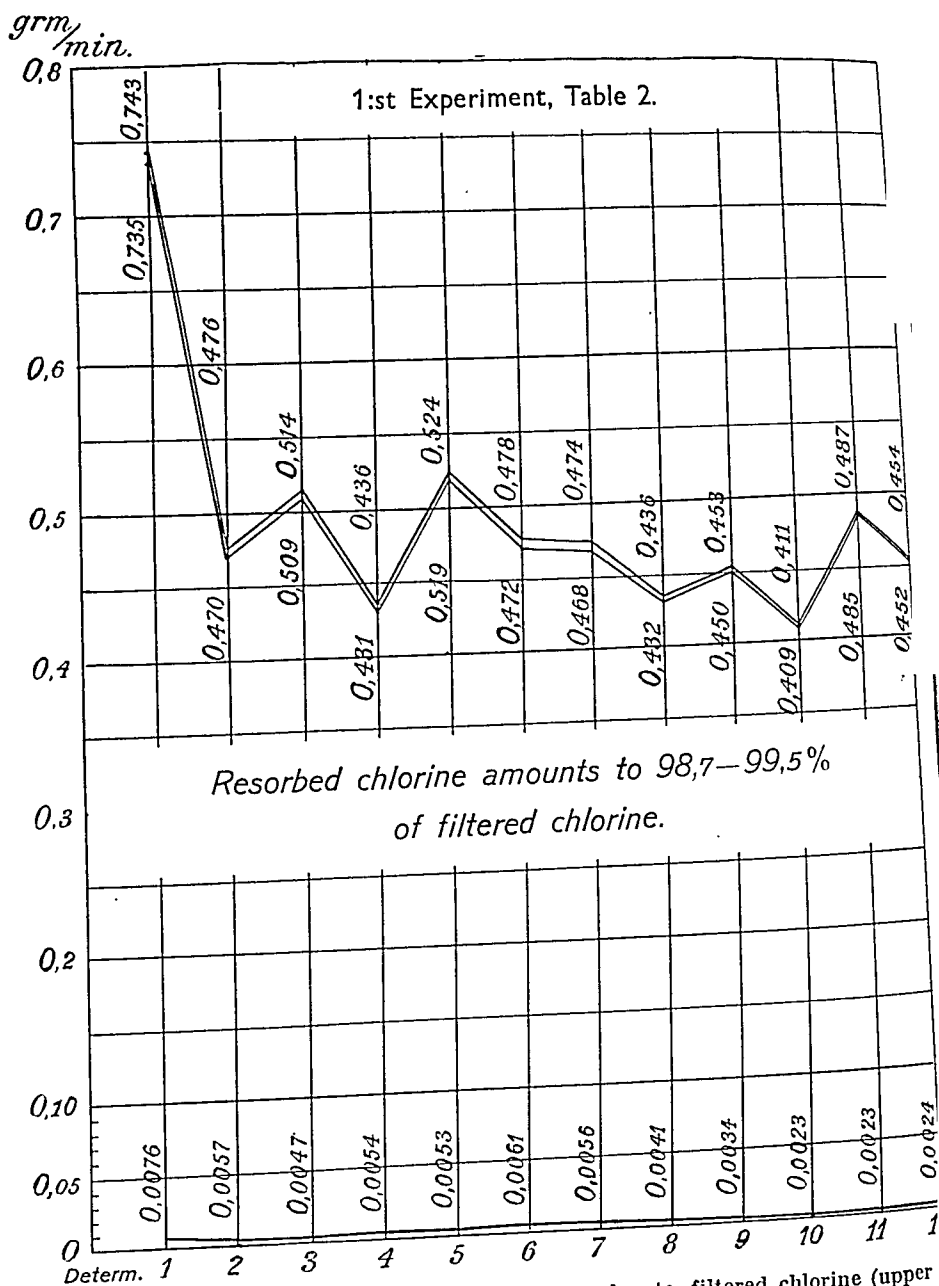
Fig. 5. The two almost parallell curves denote filtered chlorine (upper curve) and reabsorbed d:o (lower curve). Curve near the zero-line denotes excreted chlorine; all curves represent Grm per minute.

Chlorine.
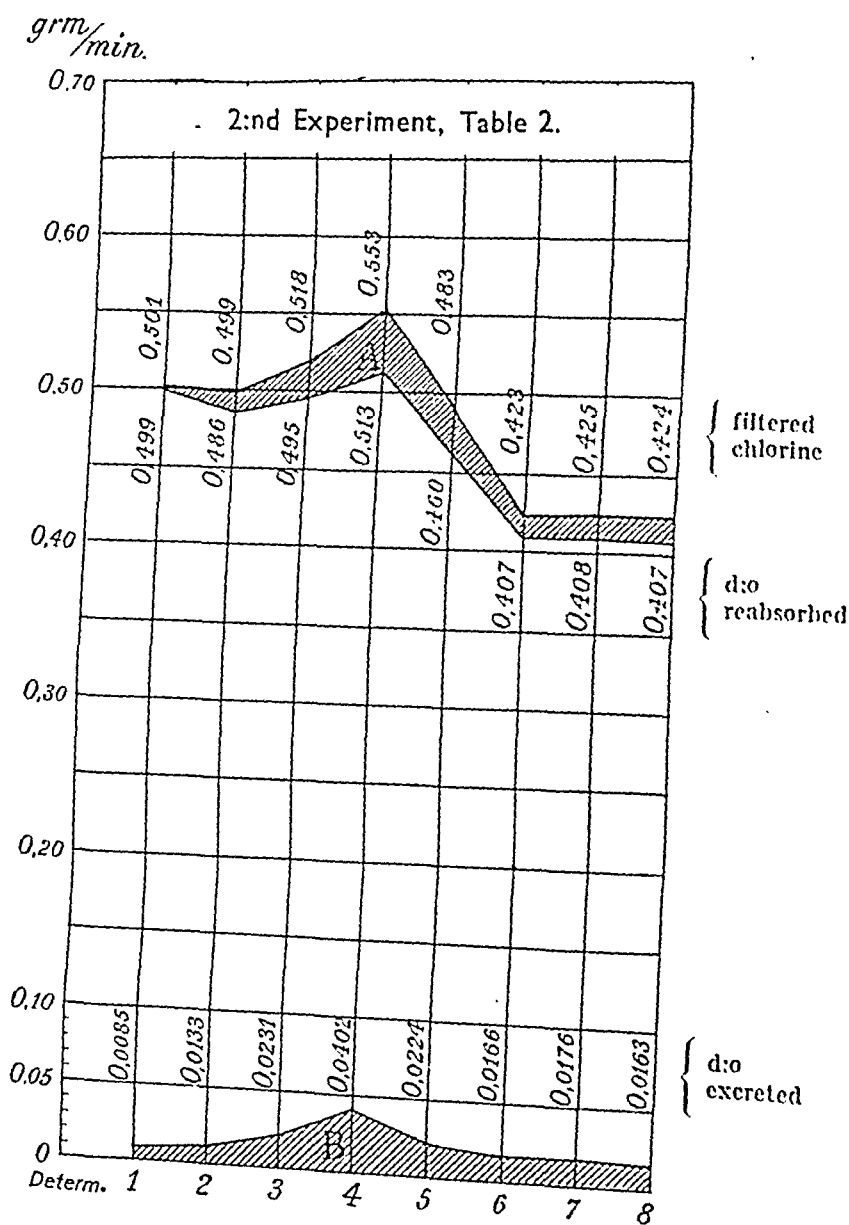
Fig. 6.   Curves and units as in fig. 5. The Areas A and B equal the excreted chlorine.

Chlorine.
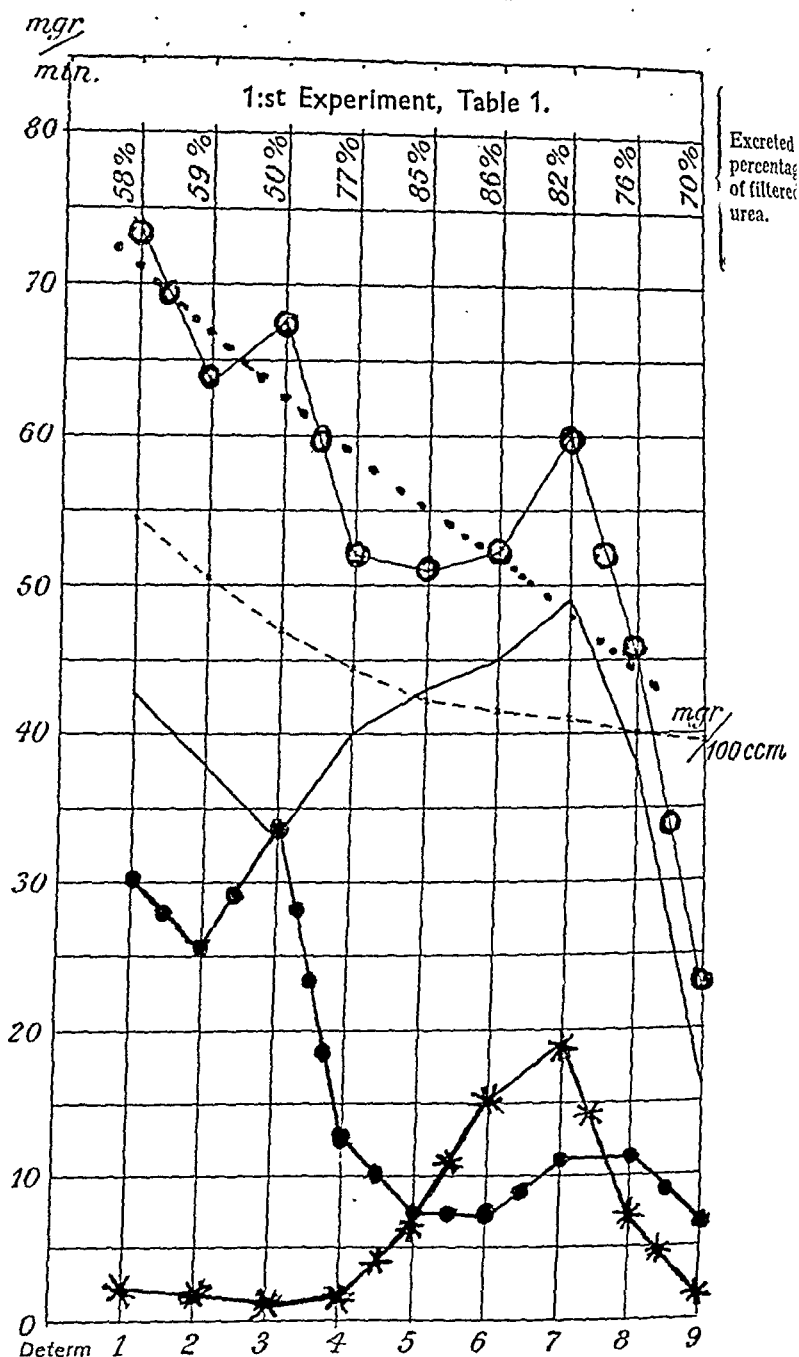
Fig. 7.   o o o filtered urea in mg/minute; •••• mean filtration of urea, mg/min; — — — plasma urea in mg/100 cm³; ———— excreted urea mg/ min; •—•— resorbed urea mg/min; ✳✳✳ water excretion cm³/min.

Urea.

which with the exception of the selected ones always were performed and reported far too perfunctorily for allowing any supplementary recalculation at all.

Preliminary discussion of some adequate renal records.

We will now consider the 35 adequate creatinine-tests, just mentioned. There can be no question in this paper to enter into a complete and detailed exploration of all the particular problems, which adequate reports of the chief partial processes of the kidney unveil. A more detailed·analysis is contained in my book »Integrative Natur der normalen Harnbildung» and I hope to give a synopsis of these matters in following papers in this journal.

My summarizing remarks here are only intended to emphasize the fact, that a mere furtive glance at a number of adequate creatinine-reports and corresponding diagrams suffices for revealing several circumstances, which are rather important themselves, and which,. moreover, rather decidedly show the way for further detailed analysis of renal function.

Above I submit four series of creatinine-tests, performed by Rehberg on a healthy Danish male (Rehberg himself). The tables were first published in Biochem. J. 1926, vol. 20, p. 461—482, where Rehberg first described his test. I have found them exceedingly important and useful, and have republished them in both my renal monographs (Principles p. 684—87; integr. Nat. d. norm. Harnbild. p. 171—73). The diagrams are from Integrative Natur der normalen Harnbildung p. 174—86. The four experiments are briefly ˙described at the bottom of the tables.

The following remarks are obvious at once from these tables and diagrams.

1) Both as regards the urinary excretion of water and of chlorine, *the amounts excreted with the final urine are independent of the absolute level of glomerular filtration as well as of the absolute level of tubular reabsorption.*·

Increases or restrictions of the absolute amounts filtered in no way correspond to increases or restrictions of the urinary water or chlorine. Nor does absolutely increased or lessened tubular reab-

sorption cause urinary water or chlorine to decrease resp. to increase in amount.

2) *The urinary amounts* of both water and chlorine *depend instead on the relative relations of the filtered and reabsorbed amounts.* Urinary water excretion *increases* with increasing interdistance between the two curves for filtered and for tubularly reabsorbed water, and it *decreases* when the two curves draw closer together. The same applies to the filtered, reabsorbed, and finally excreted amounts of chlorine.

3) *The above two points are, in fact, quite axiomatic.* A quantity, defined as the difference between two factors, can increase or decrease *only* in accordance with the said difference; it remains necessarily quite unaffected by all such fluctuations of the said factors, that are *not* accompanied by any changes of that difference. If

$$U = F - R$$

then U will remain quite unaffected by the *absolute level* of F and R and by all fluctuations thereof; U can change *first* when the expression F—R changes, *i. e. first* when F and R *vary relatively to each other.*

This evident consequence of the simplest mathematical considerations has been a real stumbling-block even to many modern renal physiologists (cf. below).

4) *The urinary amounts of water and chlorine depend thus on the difference between the resp. amounts filtered and reabsorbed,* and are restricted or augmented corresponding to decreases or increases of that difference. We see plainly from the above tables and diagrams, that *this difference regulates itself according to the varying requirements of what may be called the »excretory situation».*

Thus in the 1st experiment of table 2 copious water drinking is begun at 12.50; the said difference begins to increase already at the following determination (determ. 4, table 2, col. V & VI; fig. 3 determ. N:r 4); it *increases still more* when the dilution of the blood becomes more apparent (table 2, col. VIII); the maximal increase coincides with the maximal blood-dilution; the gradual removal of excess plasma-water (col. VIII) causes water filtration and reabsorption to differ somewhat less towards the

end of the experiment. 2.4 litres were excreted between 1.09 and 4.42 o'clock. 3 litres had been drunk between 12.50 & 2.17.

We abstain from similar comparisons between the exigencies of the »excretory situation» for water and chlorine and the resp. filtrative-reabsorptive differences in the three other experiments of tables 1 & 2, and pass over to the following most important question.

[| 5) Does the »excretory situation» influence glomerular filtration or tubular reabsorption, when the filtered and reabsorbed amounts in this way deviate from each other resp. draw closer together, i.e. when these amounts vary relatively to each other? Is the interval, the interdistance, between the filtration- and reabsorption-curves moderated by means of some factor of the »excretory situation» moving the filtration curve to the appropriate distance from the reabsorption curve? Or is it on the contrary, so that the reabsorption curve is made to move into the appropriate place relatively to filtration?

This question is exceedingly important, because its answer determines, whether important regulatory renal mechanisms are localized in the glomeruli or in the tubules. The same answer is also of great importance as regards the nature of such regulatory processes, because glomeruli and tubules perform quite different functions, work under rather different conditions, and are differently influenced by several factors. Definite localization of a mechanism regulating the excretion of such important threshold-bodies as water and chlorine, and subsequent analysis of its finer details, will, moreover, deepen our insight into renal matters so that most of our conceptions of kidney problems will be affected thereby.

6) The question sub 5) cannot be settled completely in a preliminary discussion of the above tables and diagrams; a good deal of further evidence and much detailed discussion is required for this. The table 2 exhibits in col. XII a phenomenon, however, that is *highly suggestive of a tubular localization of the mechanism for regulating the renal water- and chlorine-excretion.*

This phenomenon is *the remarkable changes of the relative proportions of reabsorbed chlorine and water.* Thus in the first experiment of table 2, the proportion between the chlorine and the water of the tubular resorbate rises from 368.5—371 mg per 100 cm³ prior to the waterdrinking to 411 —413 mg per 100 cm³ when the water diuresis is maximal or nearly so. The proportion then gradually falls to 395 mg per 100 cm³ during the last

three determinations of the experiment, when the diuresis abates to about half its former maximum. These changes of the said proportion are also simultaneous with onset, maximum, and regress of the blood-dilution consequent upon the drinking of 3 litres of water.

The relative positions of the filtrative and reabsorptive water-curves must be regulated by the tubules and must depend on the degree of completeness with which the tubules reabsorb the filtered water. The glomerules always exude water and chlorine in the proportions of the plasma, because the glomerular fluid is an ultrafiltrate from the plasma and all filtrable constituents have identical concentrations in the two fluids. Urinary water increasing high above, and urinary chlorine falling far below the proportional amounts of water and chlorine in simultaneous plasma and simultaneous glomerular fluid *cannot therefore be due to anything else than* to lessened completeness of tubular water reabsorption or to increased completeness of tubular chlorine reabsorption, and the «chlorine concentration of the resorbate fluid» must in any case rise. When the process of glomerular filtration once has been admitted, *it follows in other words axiomatically, that production of the dilute and abundant urine of the discussed experiment implies a change in the resorptive activities of the tubules* and is due to this change. The choice is only between the two alternatives: do the tubules reabsorb filtered water less completely than before, or filtered chlorine more completely? The first alternative is the obvious one, because water increases mightily in absolute amount in the urine of the discussed experiment (table 2, col. IV), whereas neither the absolute amount of urinary chlorine nor the degree of completeness of tubular reabsorption of filtered chlorine undergo any obvious changes (table 2, col. X, XIII, XIV; fig. 5). There are certainly some minor changes in both the absolute amount of urinary chlorine as well as in the degree of completeness of tubular chlorine reabsorption as is unavoidable in a prolonged experiment. It is obvious at once, however, that the enormous water diuresis recorded cannot be derived from these minute deviations of a chlorine excretion so regular that it corresponds to the practically straight line at the bottom of fig. 5.

Just as excess of water in the plasma causes tubular water reabsorption to become less complete, excess of plasma chlorine lessens the completeness of tubular chlorine-reabsorption. The second experiment of table 2 illustrates this. In this experiment 10 g NaCl were taken by the mouth at 9.53 o'clock and again 10 g at 11.13. *Plasma chlorine* has already risen to 388 mg per 100 cm³ in the first bloodsample (11.01—11.49), attains its maximum 398.5 at 12.32—1.16, and falls gradually to 382 at 4.0—4.41 o'clock. *Urinary chlorine* (col. X) is apparently somewhat augmented already in the first determination, rises more in the following; its maximum is simultaneous with the maximal level of plasma chlorine; it then falls off, but has not returned to normal at the end of the experiment (fig. 6). *The lessened completeness of tubular chlorine reabsorption*, which causes the increased renal output of chlorine, is very obvious in col. XIII (table 2); the minimal completeness corresponds to or occurs a trifle later than

the maximum of the plasma chlorine. Development and regress of that incompleteness parallel development and regress of the plasmatic chlorine excess, although the parallelism appears less accurate in the later half of the experiment, probably owing to the 600 cm^3 of water drunk at 1.10 o'clock.

This lessened completeness of chlorine reabsorption is, finally, due to some factor operating .on or influencing the tubules. Col. XII shows how the »percentage» of resorbate chlorine varies from one determination to another and always is kept well below simultaneous blood and filtrate chlorine concentration (cf. 1st exper. of table 2, where resorbate chlorine-conc. was but a trifle lower than filtrate conc. prior to, and well above the latter after drinking water).

7) *Several a-prioristic considerations lend further support to the idea, that the tubules are charged with the task of regulating the relative rates of the filtered and the reabsorbed amounts of water, chlorine, and several other urinary constituents*, that the tubules in other words regulate the urinary excretion of these substances.

We have to consider the fact, that *glomerular filtration precedes tubular reabsorption in time as well as in space;* glomerular filtration constitutes only a *very preliminary measure* in urinary formation, by means of which a large and variable quantity of raw material (the filtrate fluid) is presented to the tubules for further elaboration into final urine. In fact, the glomerular filtrate fluid consists just of plasma, that is deproteinized completely in the healthy kidney during the process of filtration, whereas the deproteinization may be defective in the diseased or traumatized organ. The composition of the glomerular filtrate is identical with that of the plasma in every other respect.

Whereas the glomeruli just extract from the blood the raw material for urinary formation, the tubules work up this material and transform it into urine. The tubules execute this by means of reabsorbing back into the blood the excessive amounts, in which most urinary constituents are contained in the very great volume of deproteinized plasma filtered in the glomeruli. This causes profound changes in both the composition and the amount of the fluid left back in the tubules for final excretion. Thus, just over 99 % of the filtered water is usually reabsorbed, and 88—89 % are still reabsorbed even when water diuresis is excessive and amounts to some 15—20 cm^3 per minute (20 cm^3 per minute equals almost 30 l in 24 hours; cf. tables 1 & 2, col. IV & V). Very much the same applies to chlorine (tab. 2, col. XIII & XIV), *i.e.* chlorine of the final urine amounts to only a very small fraction of the chlorine filtered (usually 0.5—1 %, rising to a little over 7 % during very pronounced chlorine diuresis).

Similar proportions between the filtered, reabsorbed, and finally excreted amounts are, indeed, usually met with *in the case of all threshold bodies.* Their plasma concentrations are seldom far above their resp. thresholds, and only the small fraction above the threshold passes over into the final urine.

As these bodies are filtered in the glomeruli in concentrations identical with their plasma levels, only a correspondingly small fraction of their filtered amounts can obviously escape tubular reabsorption. The whole of their filtered amount will be reabsorbed in the tubules, if their plasma concentration is below the threshold level, as is normally the case with glucose.

It challenges imagination to think, that glomerular filtration possibly could serve to regulate the urine's content of water and other threshold bodies. The filtrate formed by the glomeruli is but the raw material of the final urine and it has to undergo drastic changes in respect of water and all other threshold bodies in the process of transformation into urine. These profound changes are executed by the tubules, and there is certainly nothing improbable in the idea, that the tubules, who in any case are charged with the task of effecting these changes, also have the function of determining, how far the changes are to proceed. Those renal parts, which turn the raw material of the urine into the finished product, are a priory more likely to be responsible for the characters of the finished product than those parts of the kidney that merely extract the raw material from the blood.

In the same direction points also the obvious fact, that it is far easier for a later process to moderate itself relatively to an earlier one, than it is for an earlier process to accommodate itself to a following one. The heart, for instance, thus regulates its beats according to exigencies existing prior to or during the beat, and not according to exigencies arising first after the beat. It would be rather strange, indeed, if the difference between for instance filtered and reabsorbed chlorine would be regulated by means of chlorine being filtered in the glomeruli in quantities which at any given moment exceed in the required degree those variable quantities of chlorine that the tubules are going to reabsorb a moment later.

A further number of general reasons pointing in the same direction is contained in chapter 8 of my »Integrative Natur der normalen Harnbildung» (p. 227—48, esp. p. 238—43). The quoted chapter concerns the very great number and the lability of the various physiological factors that influence the volume of glomerular filtration; most of these factors vary, further, quite independently of the various exigencies of the »excretory situation»; they are, moreover, generally of a nature, utterly unable to follow the fluctuations of any particular urinary constituent's »excretory situation» and still more unable to moderate themselves according to »excretory exigencies» of a severalty of urinary constituents.

This causes fluctuations of the filtrate volume that are quite independent of the »excretory exigencies» of the urinary constituents; as the filtered amounts of these are the products of their plasma concentrations and the filtrate volume, the filtered amounts of every such constituent will necessarily also vary independently of the exigencies of the excretory situation. This renders glomerular filtration unsuitable for every kind of precise regulation of the urine, i.e. unsuitable for regulating the urinary output of water and other threshold bodies.

This unsuitability is clearly brought out by a comparison of the simultaneous filtration curves of figg. 3 and 5. The two curves are very similar, almost congruent. Yet the curve of fig. 3 denotes the filtered amounts of water, of which a great excess (3 l.) is drunk during the experiment, and the renal excretion of which therefore is very much augmented. The filtration curve of fig. 5 refers to chlorine which is excreted very uniformly throughout the experiment in small quantities that only very gradually undergo certain minute changes (table 2, col. X); this is an excretion entirely conforming to the facts, that no chlorine was taken before or during this experiment, and that no excessive amount of chlorine was present in blood or body. In the first experiment of table 2 the close similarity of the two simultaneous filtration curves thus contrasts strikingly with the wide differences between water and chlorine in respect of both the urinary excretion as well as of the »excretory exigencies« of each; this shows clearly that glomerular filtration neither is suitable for nor is instrumental in regulating the renal excretion of water and chlorine.

Similar remarks apply also to the remaining experiments of tables 1 and 2 as far as water and chlorine are concerned, as is easily seen from the tables and figures.

The excretions of treshold bodies and waste-products compared.

The above considerations obviously indicate that *the kidney regulates the excretion of threshold bodies, inclusive water, and waste-products differently.* Whereas the excretion of the threshold-bodies must aim at maintaining the threshold, *i.e.* at maintaining certain plasma levels as constant as possible, the excretion of the waste-products follows the rule: the more that is excreted the better, and the precise level of their plasma concentrations is a matter of small concern provided it is kept fairly low.

Extensive tubular reabsorption of glomerularly filtered waste-products would obviously only serve to vitiate the above rule; the finally excreted amount of any substance will obviously be a higher fraction of what the unit volume of blood contains, the less tubular reabsorption reduces the amounts filtered by the glomeruli. Tubular reabsorption has also a more or less subordinate rôle during the renal excretion of waste-products. Thus, none of the filtered creatinine is normally reabsorbed, and some 40—50%, or in some circumstances much more, of the filtered urea escapes tubular reabsorption and passes over into the final urine. Other waste-products, and a great number of plasma-foreign substances, for instance several carbohydrates, resemble creatinine or urea or occupy an intermediate place as regards reabsorption in the tubules (cf. my preceding paper in this journ.). Some 20 % of the creatinine of the renal

was paralleled by similar fluctuations of the other amount. The finally excreted quantity did instead depend on the difference between the filtered and reabsorbed amounts. Reasons were also given, indicating that the tubules somehow determined the exact order of the filtrative reabsorptive differences of the threshold-bodies.

The tubules cannot possibly execute a similar regulating function in the case of the waste-products. Tubular influence on the excretion of substances, that like *creatinine* are not reabsorbed at all, is of course nil. The urinary amounts of such substances equal the filtered amounts, *i.e.* they equal the product of the filtrate volume and the substance's plasma concentration. If the filtrate volume remained constant, the excreted amounts of such substances would obviously be directly proportional to their plasma levels. As the filtrate volume fluctuates independly of the creatinine level of the plasma, *the filtered and excreted creatinine-amounts will also deviate somewhat from a strict proportionality to the plasma level of the creatinine.*

This is very obvious from the above two diagrams, which show the filtered amounts of creatinine in mg per minute (the upper curves) and the plasma conc. of creatinine in mg per 100 cm^3. The diagrams refer to the four experiments of tables 1 & 2. We see that the creatinine filtration (and excretion) *sometimes parallels the plasma level fairly closely* (curves 1_2 and 2_2, especially 1.), *but that in other cases* (curves 1_1 & 2_1) *deviations become apparent;* there is here only a somewhat approximate parallelism between the level of the plasma creatinine and the general direction of the creatinine filtration curves (the dotted lines).

Turning now to *such waste-products, that like urea are subjected to some degree of tubular reabsorption,* we see from fig. 7, that filtered urea certainly parallels the plasma concentration of urea in a rough way in the first six determinations (dotted line represents an average of the actually filtered amounts). The actually filtered urea, however, is subjected to positive and negative deviations from this rough general parallelism, just as filtered creatinine.

The subsequent tubular reabsorption of part of the filtered urea is in no way able always to counterbalance these deviations. On the contrary, it may cause urea excretion to diverge still further from parelleling the urea level of the plasma. Contrary to the tubular reabsorption of threshold bodies, which regulates itself strictly according to the plasma's content of the substance in question, the tubular reabsorption of urea is largely influenced by the renal behaviour towards quite another urinary constituent, viz. water. It has long been known, that water diuresis augments urea excretion. The tubular reabsorption of urea is closely linked up with that of water; when less of the filtered water is reabsorbed in water diuresis, less of the filtered urea is reabsorbed as well, and more goes over into the final urine. This is well brought out in fig. 7 (p. 72). Absolutely, as well as relatively to the filtered amounts, urea reabsorption decreases and urea excretion increases corresponding to the strongly augmented water excretion during period 4—9. Neither the

falling off in urea reabsorption, nor the analogous large peak in urine urea correspond in any way to the plasma level of urea or to the organism's requirements as to its excretion.

Briefly we may say, that the renal excretions of threshold bodies, inclusive water, on the one hand, and the excretion of waste-products, on the other, are regulated in rather different ways. The differences may be summarized thus:

Threshold bodies.

Only the fraction above their threshold in plasma is excreted.

Only a small fraction of their filtered amounts passes over into the final urine, the rest being reabsorbed by the tubules. The R. E. R. is low.

The difference between the filtered and the reabsorbed amounts is regulated in very strict conformity with the organism's requirements as to the excretion of the particular threshold bodies. To all appearances the tubules are charged with regulating the said difference. The excreted amounts equal that difference, and are independent of the absolute amounts filtered or reabsorbed. This means that the threshold bodies normally are excreted in amounts, that strictly correspond to the organism's requirements as regards the maintenance of the particular thresholds.

Waste products.

As much as possible is excreted.

Tubular reabsorbability is much lower; the whole or in any case a large part of their filtered amounts is excreted and the R. E. R. is high.

The regulation of the excreted amounts is very much a question of how much that is filtered of the various waste-products. This at all events is the case in respect of bodies that are not at all reabsorbed in the tubules (creatinine). In the case of to some degree reabsorbable waste-products (urea), tubular reabsorption influences the amounts excreted, but does not influence them in a regulating sense, i.e. according to what the organism requires to be excreted of the particular waste-product. When waste-products are reabsorbed by the tubules, the process is often just a collateral phenomenon to tubular reabsorption of some threshold body

As will be discussed in a following paper, the treshold bodies differ from the waste-products also in that respect, that they have no characteristic clearances; this difference depends on the different tubular resorbability of threshold bodies and waste-products, and on the different ways in which the kidney regulates their excretion.

and varies with the latter independently of the waste-product's plasma level.

The urinary amounts of the waste-products cannot therefore always correspond strictly to their plasma levels, as neither the filtered nor the reabsorbed amounts, nor the difference between them vary in strict conformity with the plasma level. These deviations may under circumstances even be large enough temporarily quite to annul the rough general para lelism between the excreted amounts and the plasma lev.1 of the waste-products.

It is outside the scope of this paper further to enlarge upon these questions. I have discussed these matters extensively in my monograph »Integrative Natur der normalen Harnbildung». It will also appear from subsequent papers in this Journal that the above-mentioned characteristic differences between threshold-bodies and waste-products are rather fundamental for a detailed study of how the kidney regulates the excretion of various urinary constituents.

It is indeed *axiomatic, that the kidney must treat threshold-bodies and waste-products rather differently.* However, no aspect of the question, why and by what means the kidney is able to effect this different treatment can be properly elucidated, as long as authors consistently neglect the most important partial kidney function, namely the tubular processes, which are responsible for transforming the glomerular volumes of mere deproteinized plasma into finished urine.

As a matter of fact, the whole physiological kidney literature therefore contains no acceptable suggestion useful for explaining this different treatment of threshold-bodies resp. waste-products. There are certainly some tentative statements from the time of

the »renal secretion theory» to the effect, that the kidney begins to secrete the threshold-bodies first when their threshold is exceeded in the plasma, whereas it secretes waste-products as soon as they are present in the blood at all. Apart from the fact, that such statements are based upon altogether erroneous conceptions of the nature of the renal excretory processes, statements like these convey no information but merely restate the question in other words.

The »amplifying» powers of the kidney.

There remains, finally, another matter, where a mere glance at the tables 1 & 2 suffices for explaining a fundamental characteristicon of renal activity, namely *the »amplifying» powers of the kidney.*

The kidney is a most important regulator of the water and of numerous salts of the plasma in addition to being the chief excretory apparatus for non-gaseous metabolic waste-products. It is nothing less than *essential for the kidney in this double capacity* to be provided with means to change the urine's composition to degrees far in excess of those changes in the plasma's composition which are to bee corrected.

If, for instance, plasma chlorine exceeds its normal level, urine chlorine must be rised to a still higher concentration. *If the urine did not become richer in chlorine* than the plasma, *the kidney would obviously be unable to correct the too high chlorine concentration of the plasma;* however much the renal chlorine excretion was augmented, absolutely, the kidney would also remove a proportional amount of plasma water, and the relative proportions of the plasma's chlorine and water could not possibly be normalized again. Normalization implies removal *of relatively more* chlorine than water from the plasma; the richer the urine becomes in chlorine the quicker will this normalization occur and the more effectively will the kidney correct the chlorine-excess of the plasma.

We see also from tables 1 & 2, that the recorded changes in the plasma's composition are reflected in changes of the urinary concentrations, that are *high multiples* of the former.

Thus, when 3 l of water were drunk in the 1st experiment of table 2, plasma chlorine fell from 371 mg per 100 cm³ (average of the 3 determin. prior to water drinking) to 362 mg at the lowest, i.e. plasma chlorine fell to 97.6 % of its former concentration and plasma water increased so that the 371 mg chlorine earlier contained in 100 cm³ of plasma became dissolved in 102.4 cm³, when the plasma dilution was maximal. The water of the urine, on the other hand, does not increase by as little as a trifling 2.4 % of its former quantity; it amounts on an average to 1.15 cm³ per minute during the 3 first observations, and rises to 17.6 cm³ per min. during maximal diuresis, or to 1530 % of its former order. *The water excess in the urine is some 600 times stronger than the water excess of the plasma.*

Similarly, *plasma chlorine* in the 2nd experiment of table 2 after the ingestion of 20 mg sodium chloride rises to an average of 391 and to a maximum of 398.5 mg per 100 cm³ — an increase of aver. 20 and max. 28 mg/100 cm³ as compared with the 371 mg/100 cm³ in the 3 first determinations of experiment 1 of the same table. The concentration of *urinary chlorine* rises from 563 mg per cent (the average of determin. 1—3 of the 1st exp.) to a maximum of 1061 mg per cent, and it remains very near this figure during most of the 2nd experiment. This is an increase of almost 500 mg/100 cm³ in the conc. of the urinary chlorine, a 20-fold higher rise than that of the plasma chlorine.

Not only threshold bodies like water and chlorine *but also waste-products* like for instance creatinine and urea display also these powers of the kidney considerably to magnify in the urine insignificant fluctuations in the plasma's composition. The phenomenon is certainly in some aspects less striking in the case of waste-products, and it is not evident at all in respect of their absolute amounts in the urine. *The absolute amounts of the waste-products in the urine vary approximately proportionally to their amounts in the blood,* as was mentioned on above.

The very fact, on the other hand, that waste-products are excreted in absolute amounts which, subject to certain deviations, are roughly proportional to their plasma levels, this fact implies, that their *urinary concentrations* undergo drastic changes when their plasmatic concentrations vary with a few milligrams per 100 cm³ (creatinine) or with just some 20—40 mg/100 cm³ (urea). Thus urea concentration is 1000—2000 mg/100 cm³ higher in the first 4 urines of experiment 1, table 1 (i.e. prior to the water diuresis) than in the urines of the following experiment. The urea concentrations of the corresponding plasmas differ only by some 20—40 mg per 100 cm³.

This contrast between the insignificant changes of composition of healthy persons' *plasma and the incomparably wider changes in the amount and composition of the resulting urine* is nothing peculiar to the cases recorded in our tables 1 & 2.

It is indeed characteristic of the plasma of healthy subjects that its composition remains almost constant in spite of the con-

siderable variations of the metabolism that occur during rest and more or less intense muscular work, in thirst and hunger, or during and after more or less hearty meals. Intestinal action, transudation and respiration may also deprive the body of plasmatic salts and water in quantities that may be very large on one occasion and next to nothing on another.

The findings of our tables 1 & 2, viz. that even ingestion of nauseating quantities of urea, NaCl, and water cause but rather insignificant changes in the plasma composition, these findings agree entirely both with a wide general experience and with the results of special investigations. Govaerts and Cambier (cf. discussion and table of results in Integrative Natur der normalen Harnbildung p. 635—37) have thus examined the degree of the plasma's dilution after water drinking. They estimate the maximal dilution after drinking 1 liter of water to an addition of 10—11 cm³ of water to every liter of plasma; i.e. to an increase of 1 % of the plasma water. This agrees remarkably well with our table 2, where drinking of 3 litres of water caused plasma water to increase with maximally some 2.4 %. The plasma was diluted relatively somewhat less here than in Cambier's cases, as the 3 litres were drunk far slower than the 1 liter in his experiments; hence plasma water is augmented only by 2.4 % in our table 2 instead of by 3—3.3 % corresponding to Cambier.

We have enlarged somewhat extensively upon the kidney's faculty to react on minute changes of the plasma's composition with most considerable changes in the amount and composition of the urine. We have desired to emphasize *how powerful this faculty is in healthy kidneys,* and to emphasize the very great functional importance of this faculty. *It is fundamental for the kidneys efficacy as an organ eliminating waste-products and correcting deviations of the threshold-bodies from their plasma thresholds.* The more pronounced this faculty is, the quicker will the kidney be able to eliminate all excesses of waste-products and threshold-bodies from the plasma, the more effectively will it restrict the excretion of a threshold-body that threatens to fall below its threshold level in the plasma. We have also seen from tables 1 & 2 that the healthy kidney possesses this faculty to a very high degree.

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How is then this fundamentally important renal faculty to transform the more or less insignificant plasma changes into such powerful changes of the urine to be explained?

A mere glance at tables 1 & 2 and figures 1—7 suffices to show that *the chief component processes of urinary formation undergo no drastic quantitative or qualitative changes* when the kidney thus transforms the minute plasma variations into the incomparably more pronounced urinary variations.

Thus the *composition of the glomerular fluid* varies no more than that of the plasma; the glomerular fluid is plasma deproteinized and contains all filtrable substances in the same concentrations.

If we regard *the tubular resorbate* as a composite fluid [1], we find that its composition varies just as little as that of the glom. filtrate or plasma.

Thus in *the 2nd experiment of table 2* resorbate chlorine concentration (col. XII) varies between 372 & 389 mg per 100 cm³, and filtrate chlorine conc. between 381 & 398 (col. VIII). Average chlorine concentration in the resorbate of this exp. is 381, and average chlorine concentration in the filtrate is 391 mg per 100 cm³. The corresponding figures for determinations 1—3 of the 1st experiment of table 2 are 370 and 371 mg per 100 cm³; that is to say, average resorbate chlorine concentration in experiment 2 deviates less from the normal than average filtrate chlorine concentration does.

In *the 1st experiment of table 2* the concentration of resorbate chlorine rises from the 370 mg per 100 cm³ in determinations 1—3 to max. 413, or with 43 mg per 100 cm³. This is due to incomplete water reabsorption during water diuresis. The change of 43 mg is certainly larger than the simultaneous change in filtrate chlorine concentration, which amounts to max. 9 mg per 100 cm³ (from 371 to 362); even so, 43 mg per 100 cm³ is but a minute change.

Nor do we find any great fluctuations in the rates of the chief renal partial processes, if we turn to the absolute amounts of water and chlorine actually filtered and reabsorbed. We see from fig. 1—6, that *the absolute amounts of water and chlorine, that are filtered or reabsorbed*, only fluctuate within a range of ± 10 to 20 % of the respective average rates; wider fluctuations occur occasionally, but are obviously the effect of chance and do

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[1] Actually, water and electroactive solutes appear to be reabsorbed in different portions of the tubules. Urea »reabsorption» is due to some urea following the reabsorbed water. The tubules fail to hold back all the urea during the water reabsorption.

not influence the amounts excreted appreciably [1]. We have emphasized, however, that the absolute amounts filtered or reabsorbed are without influence on the excreted quantities of water chlorine and other threshold-bodies. The excreted quantities depend on how the filtered and reabsorbed quantities vary *relatively* to each other. *These relative fluctuations* are even smaller than those of the absolute amounts just referred to. We see thus from col. XIV of table 2 that the reabsorbed chlorine is 99 % (98.7—99.1 %) of the filtered amount during the earlier haft of the first experiment, and that it rises during the second half to 99.5 %. During the rather massive NaCl-diuresis of the 2nd experiment reabsorbed chlorine falls to a minimum of 92.7 % of the filtered quantity.

Corresponding calculations as regards filtered and reabsorbed water (cf. col. V & VI, tables 1 & 2) show that just over 99 % of the filtered water is reabsorbed when the urine flow amounts to the usual 1 cm^3 per minute. Some 98 % respectively 97 %, are reabsorbed when the urine's volume is doubled or trebled; even when water is excreted at the enormous rates of 17.6 or 19.25 cm^3 per minute (corresponding to over 25 resp. almost 30 litres in 24 hours), water reabsorption still amounts to 86—87 % of the quantity filtered.

A decrease in the water reabsorption with some 12—13 % (from 99 to 86—87 % of the filtered quantity) thus suffices to rise urine water up to some 1800—1900 % of its usual volume. Similarly, a decrease of chlorine reabsorption of some 6 % (from 99 to 92.7 % of the filtered chlorine) suffices for elevating the excreted chlorine from 7.5 to 40 mg per minute or up to over 500 % of earlier excretion.

                    *   *
                         *

No more than in the case of water and threshold bodies *are any large and drastic changes of the renal partial processes required for the excretion of the urine's waste-products.*

Their filtered amounts are the products of the filtrate's volume (*i.e.* the quantity of filtered water) and of their plasma concentrations. We have just mentioned that *the filtrate volume* as a rule is not subjected to any drastic changes; fluctuations, amounting to ± 10—20 % of the average filtrate volume are certainly not very large. A very great number of variable haemodynamic factors influence the process of filtration in positive and negative ways. These factors maintain together a kind of labil equilibrium (cf. chapter 8, Integrative Natur der normalen Harn-bildung), where their common resultant sways to and fro just as does a high column of objects, which a juggler builds up and balances on his head. Nor does the other factor, which determines the filtered quantities of the waste-products, *i.e. their plasma-concentrations*, vary very widely; not even

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[1] Unusually large amounts at the beginning and unusually small amounts at the end of the series of determinations (cf. fig. 1, 3, 5 & 7) may be due to incomplete emptying of the bladder before collecting the 1st resp. when collecting the last urine sample.

when rather drastic quantities have been ingested, almost equalling (urea) or surpassing (creatinine) the whole normal 24-hourly output (tables 1 & 2, col. II & VIII). *The filtered amounts of the waste-products follow in any case their plasma concentrations in an approximately proportional manner, and this requires no drastic change in any filtrative renal process.*

Certain waste-products are subject to some degree of *tubular reabsorption*, as is for instance the case with urea. In spite of the fact, that the reabsorbed fraction of the filtered urea and also the absolute amounts reabsorbed may vary a good deal (col. XI, XIV & XV, table 1; cf. figure 7), yet *no active renal reabsorptive process is required to vary its rate widely because of this.* It has long been known (cf. Integrative Natur der normalen Harnbildung, p. 256, investigations by Rehberg) that urea is not reabsorbed actively by the tubules, but diffuses out of the urine together with the water actively reabsorbed. The tubular walls are not quite impermeable to urea and are unable to prevent that some urea gets admixed to the reabsorbed water, especially because urea has practically electro-indifferent and rather small molecules and because water reabsorption in the tubules considerably increases its osmotic attraction to water. We see from col. XII, table 1, that *the degree of this admixture of urea to the reabsorbed water varies, but only within rather narrow limits:* the admixture amounts to at least 6.5 mg and does not rise above 24 mg per 100 cm^3 reabsorbed water. This is rather a narrow range in itself, and appears still more so when we take account of the vastly different osmotic pressures of the urea retained in the urine. The urines of table 1 are sometimes very concentrated and contain a high percentage of urea, and are in other observations dilute or exceedingly dilute and contain low concentrations of urea. Urea will press forward against the tubular walls with very different osmotic power, and yet the degree of admixture to the resorbate water varies but within the narrow limits mentioned. Discussing these and other particulars of urea reabsorption in much detail in chapter 9 of the Integrative Natur, we come definitely to the conclusion, that the fluctuations of urea »reabsorption» in the normal kidney apparently are not due to different behaviour of the renal epithelium towards urea and certainly not due to any marked changes in that behavior (Integrative Natur p. 288—89).

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It is simple to explain, how the kidney can form so widely different urines as in tables 1 & 2 and how it can change the excreted amounts of the various urinary constituents so drastically *although the renal processes, that cause these urinary changes, themselves vary only within rather narrow limits;* indeed the partial renal processes and factors in question vary hardly more than does the composition of the practically constant plasma. The explanation is contained

in the fact, that the three volumes of respectively the *glomerular filtrate,* the *tubular resorbate,* and the *final urine* relate to each other as 135: 134: 1.

With this average proportion between the three fluids, even minute variations of the volume or composition of one of the two primary fluids must change the urine's quantity or composition profoundly in every instance where no corresponding variation of the other primary fluid counterbalances the said variation. Counterbalanced variations, on the other hand, cannot have any obvious effect on the final urine, not even if they are marked, or indeed, excessive.

The renal power of amplification — i.e. to change the more or less minute variations of the plasma's composition into the often a hundredfold, or more than a hundredfold, stronger variations in the excretion of urinary water and solutes — *this power is just an aspect of elementary mathematical relationships.*

The minimal variations of the plasma's composition cause somehow the filtered and reabsorbed amounts of water and urinary solutes to vary relatively to each other in similar minute degrees.

These minute relative changes of the filtered and reabsorbed amounts result in very marked changes in the urine, because the rates of filtration and reabsorption are so high in comparison with the amount of final urine.

Thus, urine volume will be doubled, if water reabsorption decreases with 1 cm³ relatively to simultaneous filtration, *i.e.* if 133 instead of 134 cm³ are reabsorbed out of the 135 cm³ filtered; urine volume will rise to a tenfold multiple, if 125 cm³ are reabsorbed out of 135 cm³ filtered etc. *Yet these variations of the resorption relatively to the filtration are more or less minute compared with the rates of filtration and reabsorption;* they do not amount to more than a very small fraction of these rates.

There is no need to give more examples of how the high rates of filtration and reabsorption enable the kidney to transform small relative deviations from the normal or average rates of the renal processes even into large changes of the urinary amounts of water and solids. Any number of such instances can be adduced from the tables 1 & 2 and from the above discussion.

The importance of minute variations of renal factors relatively to each other.

We understand now, why current renal literature hardly contains anything in explanation of this faculty, which is fundamental to the kidney both as an excretory organ and as an organ with a powerful regulating influence on the plasma's composition. As a matter of fact, *renal research has been dominated by an almost universal tendency to try to derive the variations of the volume and composition of the urine from large and drastic changes of the renal partial processes instead of from changes about as minute and little conspicuous as those of the plasma's composition.*

This tendency originates in the period, when renal excretion was believed to be *a process of direct secretion*. Every theory of direct renal secretion implies removal of each secreted product from the blood in the same amount in which it appears in the final urine; this applies to the secreted products irrespectively of whether every or only some urinary substances are secreted directly. Since a direct secretory process obviously must change its rate in direct correspondence with the amount secreted into the urine, the rates of the alleged secretory processes must obviously vary enormously. On the one hand they must be able to rise to high multiples of their normal order, and on the other they must be able to restrict themselves to per cent- or per mille-fractions of that order, and the secretion must stop altogether when the substance in question disappears from the urine.

This wide variability of the alleged secretory processes is very evident also in the modern versions of the secretion theory, where tubular secretion is thought only to occur in respect of some few substances in addition to an otherwise-filtrative-reabsorptive mode of urinary formation (Homer W. Smith and his followers). The alleged additional secretion of creatinine is thus alleged to occur, or in any case to become perceptible, first in the case of exogenous creatinine, or when plasma creatinine of man and apes exceeds its normal level of 1—2 mg per 100 cm^3. This tubular secretion of creatinine is then stated to rise in proportion to further elevation of the plasma creatinine, until a level of 75—100 mg/100 cm^3 is reached, when the secretory process is believed to have reached a maximal rate of function and to be unable on further elevation of the plasma creatinine to rise higher. I have discussed these views in my preceding paper in this journal, (exp. with elevated plasma creatinine); I only wish to point out here, that they imply so wide a variability of the secretory process, that its rate ranges from nothingness to a level at least 10 times the whole normal creatinine excretion of the kidney.

These ideas as to the necessity for the renal partial processes to vary their rates drastically, when the urine's volume and composi-

tion changes, *were then taken over by believers in the filtration-reabsorption theory.*

Cushny, the reviver of that theory, may be excused for doing so, because no method was available at his time to examine renal partial processes in a quantitative manner. Every question concerning the rates, the variations, and the interrelations of these processes was merely an object of conjecture in his days; indeed, the very existence of filtrative and reabsorptive processes in the kidney was merely surmised and in no way proved. Considering the scanty and indirect evidence at Cushny's disposal it is not astonishing that he took over a good many unwarrantable or erronous conceptions; it is far more astonishing, that he was able to construe from such defective evidence a theory adequate as a whole, and sufficiently elastic to render modifications of its many defects possible without upsetting its main items (cf. Principles, Introduction, p. XV).

Yet it is everywhere evident from Cushny's own books, that he has not grasped the opportunities, which his own theory affords for deriving even drastic urinary changes from variations of the renal partial processes about as minute as those of the blood. To take just one instance, Cushny assumes glomerular filtration to increase by leaps and bounds during water diuresis, so that the tubules become overburdened by the excessive quantity of fluid streaming down their lumina and thus fail to reabsorb the usual amount of fluid from the filtrate.

In my Integrative Natur der normalen Harnbildung I have on frequent occasions criticized the assumed necessity of looking for wide variations of the renal partial processes.

Thus Poulsson in a large series of creatinine-tests finds even less conspicuous variations of the absolute volumes of the glomerular filtrate than, as a rule, occur in our tables 1 & 2. Convinced that renal processes *must* vary very widely, he then assumes very large variations to occur in the volume of fluid reabsorbed by the tubules, and concludes that reabsorption must fall off to about 33 % of its normal rate, *i.e.* must decrease with no less than 67 %, in order to augment the urine from 1 to 3 cm³ per minute (cf. Integrative Natur, p. 448—57, table 20, fig. 23—24). All these inferences as to the considerable depression of water reabsorption, assumed to be necessary already for such mild increases of the urinary water, are absolutely negatived by the author's own results, as soon as one makes good his almost unbelievable omission to compute the volume of fluid resorbed.

I have discussed in my Integrative Natur der normalen Harn-
bildung several other instances of this inveterate belief in the
necessity of deriving the urine's variations from gross changes of
the rates of the renal partial processes.

We shall not repeat this discussion here but pass over instead
to another striking example of the same belief, which occurs in a
paper which I have had no occasion to discuss hitherto, as it was
published the year after my last monograph. The author[1] exami-
nes the question (loc. cit. p. 180) as to whether »the increased water
excretion is related to the increased filtration rate» that has been
observed after giving chickens water in a number of experiments.

He supports his contention, that such is the case, by a kind of referen-
ce to tubular water reabsorption, that in every respect illustrates the valid-
ity of our earlier remarks concerning the inadequate manner in which
tubular functions are considered, even when they are not disregarded com-
pletely as is usually the case. Korr simply states, that »calculation of the
absolute rate of water reabsorption by the tubules in periods before and
during diursis shows that the change in urine flow is not due specifically
to a decrease in the rate of reabsorption; on the contrary more water is
reabsorbed at high urine flows than at low urine flows.» It is but a truism,
that water reabsorption must increase absolutely even during water diure-
sis, when simultaneous water filtration has happened to rise more than
corresponds to the increase in urine water as was the case in many of
Korr's experiments. *Such an absolute increase is entirely consistent with
a simultaneous decrease of water reabsorption relativery to filtration.* The
author commits in other words the usual mistake upon which we have
commented so strongly in this paper, viz. the mistake of taking absolute,
instead of relative rates and variations into consideration. Korr *never
compares the simultaneous rates of water filtration and water reabsorption
with one another*, and takes no account of relative variations of these rates;
he regards all data of tubular reabsorption as *so* devoid of interest that no
such data are reported in his paper or recorded in his tables and diagrams,
and he confines his discussion of tubular problems in the chicken to the
brief and utterly inadequate sentence quoted.

Korr finds another support for his contention, that the volume of the
urine is related to the absolute volume of glomerular filtrate, in »the fact
that the filtration rate in birds, initially at water equilibrium, is markedly
increased during water diuresis». Several experiments are mentioned where
the absolute filtration of water thus rose during diuresis to double the
average order or slightly more. In another experiment filtrate volume

[1] Irvin M. Korr, Osmotic function of the chicken kidney.   J. cell. comp.
Physiol. 1939, vol. 13, p. 175—193.

fell to 50 % of its average order after 48 hours of water deprivation; the urine was very scanty here.

The absolute filtrate volumes of these chickens have thus varied rather widely, and have ranged between half and twice, or more, of their average order. This wide variability of filtration is probably due to the drastic nature of several among Korr's experimental measures (cf. the following paper in this journ.). Korr is so strongly convinced of the importance of these gross filtration variations for regulating the excretion of water, that he states in the summary of his paper: »It is concluded that variation in the filtration rate in the bird is an important factor in the conservation of water.» This strong conviction prevents Korr from perceiving that he negatives this conclusion by the immediately following statement of his summary. »Adrenine increased glomerular filtration to rates which occur during water diuresis without, however, production of any diuresis.»

The obvious conclusion from these two sets of experiments *is that the volume of the urine is independent of even the strongest fluctuations of the absolute filtrate-volume.* This conclusion rests not only on Korr's adrenine experiments, but is also confirmed by the following statement on p. 181 of his paper. After water diuresis, »when the urine flow has nearly or even completely returned to the prediuretic level, even the lowest filtration rate may still be 100 % higher than before water was administered».

This statement, that filtrate level may well rise to twice or more of its usual level without influencing the urinary water output, is complemented by another statement on the same page to the effect that urinary water excretion may vary considerably during constant glomerular filtration. »As shown by Pitts and by Shannon, and confirmed in the present experiments, glomerular filtration in the chicken remains essentially constant over wide ranges of urine low (0.2 to 1.8 cm³ per kg per minute).»

The current ideas as to the necessity of deriving urinary changes from gross variations of renal partial processes appear so to have entrapped Kroll, as to render it impossible for him to disengage himself from them even on the strength of all the observations to the contrary, which he has made himself of himself reports.

Korr's idea, that the renal water excretion varies with the volume of the glomerular filtrate, *appears still more unwarranted if one takes the trouble to scrutinize his diagrams.*

The filtrate- and urine-volumes of chicken are represented graphically in Korr's figg. 1 & 2, 4 & 7.

In Korr's *fig. 1* the first determinations may certainly agree with his thesis: urine volume increases from 0.08 cm³ to 0.8 cm³, and filtrate volume increases from 4 to 9 cm³; *all the following determinations, however, disagree hopelessly with the same thesis.* Filtrate volume thus *falls* to 6 cm³ in the 3rd determination, while the corresponding urine volume *rises* to 1.2 cm³. In the 4th pair of determinations urine volume has *risen* still more, to 1.5 cm³, and filtrate volume has *fallen* to about 5.5 cm³. Passing to the 5th pair of determinations, we see the two volumes again

moving in opposite directions: urine volume *falls* to sligtly below 1.5 cm³ and filtrate volume *rises* to somewhat above 6.5 cm³. The volume of the urine then remains practically *constant* at the level of 1.5—1.4 cm³ up to the 10th determ., while filtrate volume first *falls* to about 5.5 cm³, then *rises* to about 6.5, and then gradually *falls* to 5 cm³ in the 10th determ. Then filtrate volume remains practically *constant*, i.e. it varies between 5 cm³ in the 10th, and 5.5 cm³ in the 13th determin; urine volume, however, falls continously from the 1.5 cm³ of the 10th to 0.3 cm³ of the 13th determination.

That is to say, the two curves of the simultaneous filtrate and urine volumes *move only once in the same direction* (both rise between the 1st and the 2nd determ.); *otherwise, they move always in opposite directions*, so that a rise of the one curve corresponds to a fall of the other, *or one of the curves varies while the other remains constant*. I cannot understand, how results like these can possibly be held to indicate dependence of the urine volume on the volume of the glomerular filtrate.

In Korr's *diagrams 2 and 7* the absolute and relative maxima and minima of the two volumes correspond better in time than in his fig. 1, i.e. the two curves move as a rule at least in the same direction at corresponding points. *These falls and rises do not correspond in magnitude, however.* In *diagram 2* the urine volume is almost constant (0.08 to 0.07 cm³ per minute) during the first 3 determinations, whereas filtrate volume varies between a little over 4 cm³, and 1.5 cm³ per minute. Urine volume then rises to 2.3 cm³ in the 4th, and to 3.0 cm³ in the 5th determ.; the corresponding filtrate volumes are both 8 cm³.

The order of these changes disagrees decidedly with the findings recorded in *diagram 1*, where the urine only rose to 0.8 cm³, when filtration reached a maximum of 9 cm³. Nor do these changes during the first 5 determinations of *diagram 2* agree with the later findings of the same diagram, because the urine curve begins after about 10 minutes gradually to fall from the peak of 3 cm³ per minute and comes down to 0.3 cm³ at the end of the experiment. Simultaneous filtration, however, falls only from 8 to 6 cm³; i.e. the filtration curve decreases far slower relatively to the diminishing urine than it increased during the first 5 determinations relatively to the then rising urine volume. How can, further, this decrease of filtration in *diagram 2* from 8 to 6 cm³ be held responsible for the restriction of the urine from 3 to 0.3 cm³, when in *diagram 1* filtration could decrease from 9 to 5.5 cm³ (determ. 2—4), and the urine yet augment itself from 0.8 to 1.5 cm³?

Similar remarks apply also to Korr's *diagram 4*. Korr's *diagram n:r 4* shows no better correspondence between the volume of the urine and the (absolute) volume of the glomerular filtrate. The urine volumes remain very small, i.e. practically constant, and never surpass 0.3 cm³ per minute, whereas filtrate volume varia between just below 3 and 6 cm³. This *diagram 4* has been commented upon in another place, (Svenska Läkartid-

ningen, vol. 41, n:r 24, Stockholm 1944) and shall not be discussed here. Korr's *diagram 4* reveals, indeed, in even more striking manner than his other figures certain very surprising pecularities as to the graphical construction of curves and diagrams, that appear to be common enough also in other Smith-ian papers. Their diagrams and curves are often not constructed to a definite system of co-ordinates, nor to uniform or otherwise always comparable scales. The *abscissae* are never defined in these diagrams, and if one reconstructs them, one is very often surprised to find the different curves of the same diagram drawn to different *abscissae* and placed in quite arbitrary relative positions. Sometimes certain curves of one and the same diagram are drawn to logarithmical while other curves are simultaneously drawn to arithmetical scales. The fact appears to be imperfectly appreciated, that small numbers appear very large, and big numbers relatively very small, if represented graphically according to a logarithmical scale, etc. etc. In fact, these graphical-analytical inaccuracies often utterly upset the mathematical significance of these curves and diagrams; they must often be redrawn altogether before being discussed, or the respective figures must be read off from the curves and then compared with one another, as has just been done above in the case of Korr's paper.

Reforms of renal research must be directed towards removal of inade-
quate experimental procedures.

In my preceding paper in this journal I discussed a number of papers advocating the substitution of inulin for creatinine in the Rehberg renal tests.

I shall not repeat here my earlier criticism of these papers. It needs only be mentioned here, that this alleged renaissance of renal research in no way is concerned with the remedy of any among those misconceptions characteristic of the usual negligent manner of performing the creatinine-test, that have been criticized here.

Save for the use of another test substance, *the inulin test is a direct copy of the earlier creatinine-test:* precisely the same factors are determined in otherwise exactly the same ways in the two tests (cf. my earlier paper). The inulin-workers have *copied the creatinine-method also in respect of the prevalent mistake among creatinine-workers of not duly regarding the tubular data.*

Taking for instance the renal excretion of water, we find in the inulin-papers no end of figures, tables, and graphs referring to the

amount of filtered water (filtrate volume), but I have in all these papers never seen the tubularly reabsorbed water quantities tabulated, nor do they appear in the diagrams. Even when the volume of urinary water is plotted on a diagram together with simultaneous water filtration, the diagrams have to be redrawn in order to render the distance between the filtration- and the urine-curve illustrative of tubular water resorption; the two curves have not as a rule been drawn to a uniform scale in the original diagrams, and they are often placed quite arbitrarily relatively to each other. If the reabsorbed water quantities in exceptional instances have been computed at all, the figures obtained are still not reported but only referred to in a general way just as in Korr's paper. Nor are the reabsorbed quantities, if computed at all, duly compared with simultaneous water filtration, not even in papers like Korr's, where the investigation is alleged to differentiate between the glomerular and the tubula influence on renal water output (cf. above). Such comparisons are confined to occasional general statements to the effect, that 124 cm³ of water must be reabsorbed, if 125 cm³ are filtered during ordinary diuresis of 1 cm³ per minute, etc.

The tubular reabsorption of other *threshold-bodies* is treated even less satisfactorily than that of water.

The tubular reabsorption of *waste-products* and *plasma-foreign carbohydrates* is certainly often referred to in the text of these papers, but the references are mostly confined to such obvious general statements as for instance, that 50 or 30 % of the filtered quantities of such substances must be reabsorbed by the tubules, when their respective clearances amount to 50 or 70 % of the clearance of the test-substance. There is no need to go further into the inadequate treatment of the tubular reabsorption of these substances; I refer to my earlier criticism of the arguments alleged to bear out inulin's superiority over creatinine as a test-substance; this criticism, indeed, is chiefly directed towards the surprising manner, in which the tubular problems of these substances have been dealt with by the inulin-workers.

Instead of applying themselves to find a remedy for the serious defects and inadequacy of the current methods of the creatinine test, *the inulin enthusiasts copy their predecessors even to the point of*

consistently repeating these very defects, and base their claims of the superiority of inulin on the fact, that inulin has a somewhat lower clearance than creatinine in some species, especially in man. This is held to indicate, that the volume of the glomerular filtrate is correspondingly somewhat lower than the figure arrived at in creatinine-tests. I refer to my earlier paper in this journal as to whether this or other observations really substantiate the alleged superiority of inulin over creatinine in Rehberg tests. I only wish to add here, that hardly any problem in the whole renal physiology is of less importance than the question, whether the volume of the glomerular filtrate is somewhat higher or somewhat less than corresponds to the average of 135 ± 30 cm³ per minute according to the creatinine-method. We have thus seen above in this paper, that the excretion of water and other threshold-bodies is independent of the absolute level of the filtration. The absolute volume of the glomerular filtration has normally some influence only on the excretion of the urinary waste products, but even here this influence is subjected to many further conditions, as will be still more evident from the paper to follow.

Synopsis.

The above remarks illustrate strikingly how little it is understood even at the present time, that the universal custom to disregard tubular functions upsets kidney research seriously and prevents profitable exploration of renal activities.

It is also obvious that even the most modern renal literature displays as imperfect appreciation *both of* the really important points of filtrative-reabsorptive kidney activity *as well as of* the real implications of Rehberg's and similar tests. Nothing shows this in a more striking manner than that an attempted reform of this test by supplanting creatinine with inulin entirely overlooks the glaring inadequacies of performing the Rehberg tests, nay, indeed copies these very defects and concentrates its interest upon such a most unimportant matter as to whether the filtrate volume is a few cm³ less than the volume indicated by Rehberg's creatinine method.

This more or less complete disregard of the tubular functions is rather surprising both because of the very great importance of the tubules for the formation of the urine, as well as in view of the fact, that Rehberg's method is equally applicable to quantitative determination of tubular as well as of glomerular prestanda. The said inadequacies are astonishing also because Rehberg himself performed his test and recorded the resulting data in a thoroughly satisfactory manner already in his original publication. That grave inadvertences have crept in afterwards may be due to the circumstance, that Rehberg's original paper was confined to a somewhat incomplete discussion of the theoretical basis of the test, to a description of its technique, and to records of the resulting data in a number of excellent tables. With exception of a few trenchant remarks on the tubular reabsorption of urea, Rehberg did not subject his results to any particular discussion, nor analyze the bearings and implications of the data obtained; this may explain, why these tests have been so imperfectly understood by most later investigators. Nor were adequately prepared kidney tables, i.e. tables giving complete tubular as well as glomerular data, ever subjected to any detailed discussion or comprehensive analysis until I attempted to fill up the blank with my Integrative Natur der normalen Harnbildung, which appeared late in 1938.

Rehbergian tests are certainly not our only means for studying the complex renal function, but they are more important than any other among the means presently at our disposal for that purpose. Adequately recorded and duly considered such tests afford, in fact, no end of information in the most divers renal questions. Together with certain other experiments the Rehbergian tests lead up to remarkably complete and detailed conceptions of renal activity; they enable us to penetrate up to, and sometimes beyond, the boarder of the individual renal cell; in some instances we arrive in regions where biology merges into physics and mathematics. We find cellular actions in the kidney, illustrative of the most general and profound laws of biology, and we can perceive, how these cellular activities combine to form an integrated function of the whole organ, in its way as accomplished as that of the brain. These matters have been discussed earlier in my »Inte-

grative Natur der normalen Harnbildung», and they will be summarized in simple form in following papers in this Journal. We have not gone into them in this rather preliminary paper, where we have merely confined ourselves to show, that already the most cursory examination of properly recorded Rehbergian tests reveals information of fundamental importance for the study of renal problems.

We find in the first place that *the urinary output of water and other threshold-bodies is independent of the absolute amounts filtered or reabsorbed. Their urinary output and its variations depend instead in the healthy kidney upon the relative relations of the filtered and reabsorbed amounts, i.e. upon how much these amounts differ.* This, indeed, is quite axiomatic, because the urinary amounts of water and other threshold-bodies are differences between the excessive quantities filtered and the but slightly lesser quantities reabsorbed; one of the principal mathematical characteristica of a difference, however, is that its magnitude is determined solely by the degree to which the differing quantities differ and not by their absolute order.

Their absolute order can influence the magnitude of the difference only in a few well-defined special instances, as when one of the two differing factors is at or near 5erd level or when it constitutes a definite fraction of the other factor, etc.

Renal physiology has consistently overlooked these axiomatic implications of elementary mathematics; up to the very last years renal physiologists have with greatest pertinacity attempted to derive the changes of the urine's amount and composition from changes of the absolute order of the partial renal processes. Having thus focussed their attention on phenomena normally of no influence on the renal output of threshold-bodies, renal physiologists have not been able to clear up the excretion of these bodies at all. All questions as to how the kidney regulates its output of these bodies remain a perfect jungle of conjecture and confusion. The paper, discussed on p. 93—96 above, shows that even as late as 1939 the regulation of renal water excretion even in one of the greatest physiological laboratories of the world was regarded as a question, whether glomerular water filtration was augmented, absolutely, during water diuresis, or whether the tubules reabsorbed less water absolutely; there was no thought of comparing water filtration and

simultaneous water reabsorption with each other, *i.e.* of studying the two processes relatively to each other.

The inveterate reluctance of renal physiologists to take due account of the tubular data has also quite prevented them from seeing, *how little the tubular and glomerular processes have to change relatively to each other in order to procure even the greatest changes in the final urine.*

This powerful effect of small relative changes of the glomerular and tubular processes *is but a simple arithmetical consequence of the fact, that the filtrate and resorbate fluids are so exceedingly voluminous in comparison with the resulting urine.* When the three volumes of filtrate, resorbate, and urine on an average relate as the figures 125 : 124 : 1 (or more correctly as 135 : 134 : 1), obviously even relatively very small changes in volume or composition of one of the two primary fluids must cause considerable changes in volume or composition of the urine. Even quite excessive changes of the urine are in fact derivable from relative changes of the renal partial processes of about as minute order as the changes of the blood.

This *amplifying power of the kidney is of quite fundamental importance for its efficacy* both as an organ removing waste products from the blood as well as in its capacity of a regulator of the blood's threshold-bodies. The kidney would be deficient in both respects if it was unable to transform the minute changes of the blood into very much stronger changes of the urine, indeed.

Far from realizing, how efficacious more or less minute relative variations of the partial renal processes really are in producing even the grossest changes in the urine, renal physiology has instead persistently tried to derive even very moderate changes in the urine fram variations of the renal partial processes, supposed to be of a high order of magnitude. This applies even to the most modern papers.

These failures of current renal research have been of much consequence. No success, but only confusion and mistakes are to be expected, indeed, from methods of analyzing kidney function, which leave the most important partial processes of the organ (the tubules) out of regard, which take notice only of little im-

portant absolute variations of the partial processes but take no account of the exceedingly significant variations of these processes relatively to each other, and which, finally, err also in that respect, that they pursue the study of gross instead of more or less minute variations of the renal partial processes. It is almost impossible to think of any kind of scientific analysis that has gone more beside the renal points.

I shall but very briefly mention some other points of this paper.

The urinary quantitities of water and other threshold bodies depend not on the absolute amounts of these bodies, that have been filtered or reabsorbed, *but depend on the difference* between the filtered and reabsorbed amount; *every complete analysis of the renal regulation of the excretion of these bodies must necessarily also embrace the question, how these filtrative-resorptive differences are regulated*. A preliminary step in every such analysis is obviously to try to ascertain, whether the filtering glomerules or the reabsorbing tubules are charged with the task of regulating these differences. It is then of great interest, that already the cursory examination of this paper, even if it does not suffice entirely to prove that the tubules are charged with this task, yet suffices to indicate this rather decidedly.

Another point concerns *the different manners, in which threshold bodies* and *waste-products are excreted by the kidney.* The renal excretion of these substances follows in certain aspects so different lines, that no conception of renal activity can be taken as valid, unless it renders these differences explicable. Although our discussion has been rather preliminary in this respect as well, yet the simple procedure to compute and tabulate the renal data properly, suffices to bring up, and to some degree also to elucidate, several points of importance as regards the kidney's different behaviour towards these substances.

From the Kommune Hospital, Copenhagen [Pathological Institute (Chief Pathologist: Svend Petri, M.D.) and the Medical Departments II (Chief Physician: H. Heckscher, M. D.), III (Chief Physician: P. Iversen, M.D.) and VII (Chief Physician: T. Bjering, M. D.)], from the Central Hospital, Randers (Chief Physician: Ole Bang, M.D.) and from the Biochemical Laboratory of Medicinalco, Ltd. (Chief: E. Jacobsen, M.D.).

Experimental Studies on the Significance of the Various Regions of the Stomach to the Antipernicious-Anemic Principle Content of the Liver (in Swine).

III. Effect of Dried Swine Stomach Preparation (Pylorin, MCO) on the Disappearance of Antipernicious-anemic Principle in the Liver following Resection of the Fundus of the Stomach. [1]

By

SVEND PETRI, OLE BANG, WILLIAM KIÆR and AAGE KJERBYE NIELSEN.

(Submitted for publication May 30, 1944).

Introduction.

In our previous investigations (1941, 1944) it has been demonstrated that elective resection of the fundus of the stomach in pigs constantly brings about a complete disappearance of antipernicious-anemic principle from the liver and that this loss — in contrast to the findings after total gastrectomy — can be counterbalanced by treatment with nicotinic acid. From this, the following conclusions were drawn: that the fundus is primarily decisive of the formation of the active liver principle, that the formation of this principle must be connected with the stomach exclusively, and that nicotinic acid — in connection with the two other regions of the stomach left by the operation (cardia + pylorus) — are of

importance to this process; in this respect the cardia is the decisive region. As to the relation between the fundus and the cardia with regard to the formation of the antipernicious-anemic principle nothing definite may be said yet, but this question is now being investigated.

During the systematic extension of these experimental studies the aim has been to elucidate the following two aspects:

1) The significance of the three stomach regions *per se* to the formation of the liver principle (through performance of the six theoretically possible, single or combined, types of resection), and

2) the possible ability of a number of substances, like nicotinic acid, to counteract the disappearance of the antipernicious-anemic principle of the liver in fundus-resected pigs — especially preparations employed in the treatment of pernicious anemia and various vitamins.

The studies reported in the following fall in the latter group of experiments: a fundus-resected pig was treated with Pylorin (MCO), and the effect of the extract from the liver of this animal was examined on 5 patients with pernicious anemia.

Material and Technique.

Experimental Animal. Total resection of the fundus was performed in the usual manner on a Danish bacon pig, (No. 131), 7—8 weeks old. In this animal a morbid pellagrous condition developed, corresponding to the lesion previously described (1942, 1943). After an observation period of 252 days the animal was treated daily for 132 days with Pylorin (MCO); the dose was 2 powders (of about 10 g) daily, given by mouth, mixed with the first portion of the morning feed. After a total observation period of 384 days the animal was bled to death. The ordinary experimental conditions, especially the diet, were the same as usually employed by us. On autopsy the liver was found microscopically to be normal. The resection of the fundus was found histotopographically to have been total. The remaining gastric mucosa (cardia + pylorus) presented no pathological changes.

Preparation of Liver Extract. From the liver of this swine some extract was prepared in the same manner as previously; as usual, 1 cm³ of Hepsol corresponds to 5 g liver.

Pernicious-anemic Patients. 5 patients were employed as test subjects — 3 women (aged 59, 73 and 83 years) and 2 men (aged 44 and 66 years) — presented clinically typical cases of the lesion and had received no treatment previously. The treatment with the experimental and control preparations has been the same in all five cases. The experimental extract (»Hepsol 2—101») was given intramuscularly in a dose of 10 cm³ on 2 successive days; after a pause (as a rule, without any other form of treatment) of 10—13 days, the patients were given the control preparation (Hepsol MCO) in the same dosage, and then they were observed for 12—17 days. After this, if required, the patients were given the supplementary therapy usually employed by the respective departments.

Results of the Treatment of Pernicious-anemic Patients with Liver Extracts from the Experimental Animal.

Case 1.

A. *N.* Woman, aged 59, Adm. to the Med. Dep. of the Central Hosp., Randers (Reg. No. 1210/43) on 2/8/43. Discharged 18/9/43.

Since childhood, repeated periods of anemia, treated with iron tablets, but never with liver preparations. Gastric achylia (free acid 0; total acidity
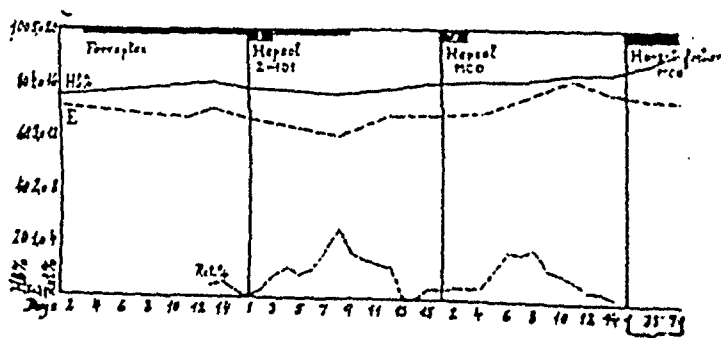
Fig. 1.

23; later, 0/14). Tongue smooth. Paresthesias present. Hemoglobin 75 %. Erythrocytes 3.55 millions. Color index 1.06. White blood cells 2880 (lymphocytes 41 %). Reticulocytes 0.9 %. Platelets 430,000. Plasma color 6. Diameter of erythrocytes about 8 μ. Megalocytosis and aniso-poikilocytosis.

Last blood examination, on 4/12/43: Hemoglobin 92 %. Erythrocytes 3.74 mill. Color index 1.23. White blood cells 3680. (lymphocytes 37 %). Slight anisocytosis.

Treatment: 1) Tabl. ferrosi tartras, »Ferroplex» DAK, 2 × 3 daily, 6/8—27/8; 2) »Hepsol 2—101», 10 cm³ intramuscularly daily for 2 days,

19/8 and 20/8; 3) Hepsol MCO, 10 cm³ intramuscularly daily for 2 days, 3/9 and 4/9; 4) Hepsol fortior MCO, 5 cm³ every week, later every 2—3 weeks (since 17/9). (Fig. 1).

Case 2.

I.C.J.L.*B*. Woman, aged 73. Adm. to Dep. III of the Kommune Hospital, Copenhagen (Reg. No. 270/43) on 26/11/42. Discharged 20/2/43. No previous treatment. (Gastric achylia.) Subicteric and subfebrile condition. Tongue smooth. No paresthesias. Paralysis agitans. Hemoglobin 41 %. Erythrocytes 1.7 millions. Color index 1.3. White blood cells 4200 (lymphocytes 38 %). Reticulocytes 1 %. Macrocytosis and aniso-poikilocytosis.

Last blood examination, on 9/2/43: Hemoglobin 78 %. Erythrocytes 3.4 millions. Color index 1.1.
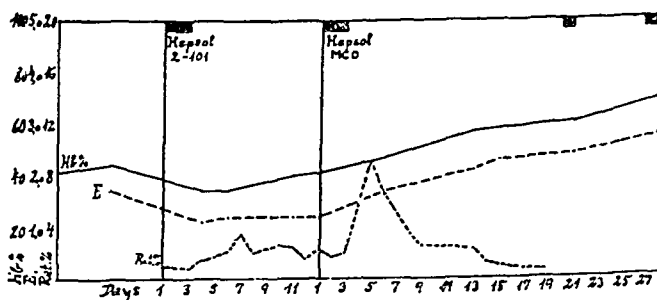
Fig. 2.

Treatment: 1) »Hepsol 2—101», 10 cm³ intramuscularly daily for 2 days, 5/12 and 6/12; 2) Hepsol MCO, 10 cm³ intramuscularly daily for 2 days, 17/12 and 18/12; 3) Hepsol MCO, 10 cm³ intramuscularly on 5/1, 12/1 and 18/1—43; 4) Hepsol fortior MCO, 5 cm³ intramuscularly on 25/1, 1/2, 8/2 and 15/2. (Fig. 2).

Case 3.

M. *M*. Woman, aged 83. Adm. to Dep. VII of the Kommune Hospital on 4/2/44. Discharged 5/4/44. (÷ Reg. No.).

No previous treatment. Stomach function not examined. Subicteric and subfebrile condition. Tongue smooth. Paresthesias present. Cystitis (colon bacilli). Myocardial degeneration. Hemoglobin 48 %. Erythrocytes 1.6 millions. Color index 1.5. White blood cells 7600 (lymphocytes 21 %). Reticulocytes 0.4 %. Macrocytosis.

Sternal puncture, on 11/2/44: Pernicious anemia (43 normoblasts and 27 megaloblasts per 80 granulocytes).

Treatment: 1) »Hepsol 2—101», 10 cm³ intramuscularly daily for 2 days, 10/2 and 11/2; 2) Hepsol MCO, 10 cm³ intramuscularly daily for 2 days,

25/2 and 26/2; 3) Hepsol fortior MCO, 5 cm³ intramuscularly (+ tabl. ferr. tart. 1 × 3 daily) on 11/3, 16 3 and 23/3, besides (from 20/3) Exopylorin MCO, 2 tubes daily. (Fig. 3).
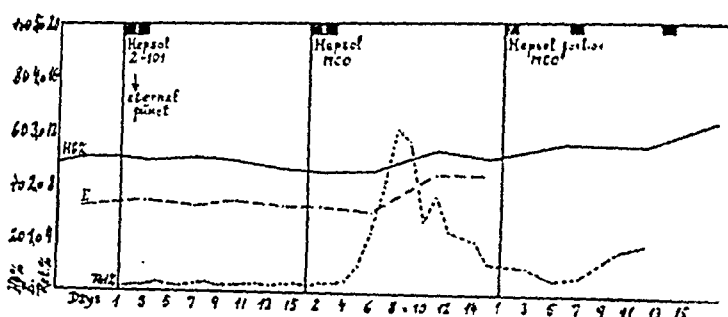
Fig. 3.

Case 4.

J.C.B. Man, aged 44. Adm. to Med. Dep. of the Central Hospital, Randers (Reg. No. 2064/43) on 13/12/43. Discharged 19/1/44.

No previous treatment. Gastric achylia (free acid 0, total acidity 11; later, 0 and 9, respectively). Subicteric and slightly subfebrile condition. Tongue smooth. Paresthesias present. Hemoglobin 37 %. Erythrocytes 1.5 millions. Color index 1.22. White blood cells 3040 (lymphocytes 48 %). Reticulocytes 3.4 %. Diameter of erythrocytes 8.5 μ. Platelets 154,000. Plasma color 10. Very marked aniso-poikilo- and megalocytosis.
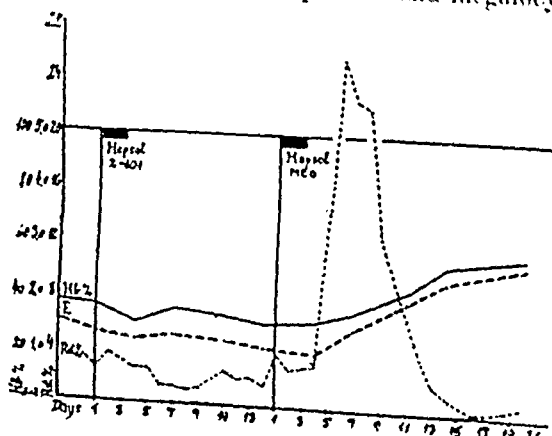
Fig. 4.

Treatment: 1) »Hepsol 2—101», 10 cm³ intramuscularly daily for 2 days, 17/12 and 18/12; 2) Hepsol MCO, 10 cm³ intramuscularly daily for 2 days, 31/12 and 1/1/44. (Fig. 4).

Case 5.

N. J. Man, aged 66, adm. to the Med. Dep. of the Central Hosp., Randers 4/5/44 (Reg. No. 917/44). Discharged / /44.

No previous treatment. Achylia (free acid, 0, total acidity 4, later

0/5); subicteric, greybrown pigmentation of the lightexposed parts of
the skin and in volæ. Tuberculosis lymfoglandularum. Hernia ingvina-
lis duplex. Hypertonia. Hemoglobin 45 %. Erythrocytes 1.73 Mill. Color
index 1.3. White blood cells 1320 (lymphocytes 39 %). Reticulocytes
1.0 %. Very marked aniso- and poikilocytosis, some megalocytes and a
few erythroblastes. Plasma color 10. Sedimentation test; 35 mm/1 hr.

Treatment: 1) »Hepsol 2-101», 10 cm³ intramuscularly daily for 2 days,
17/5 and 18/5; 2) Hepsol MCO, 10 cm³ intramuscularly daily for 2 days,
30/5 and 31/5.
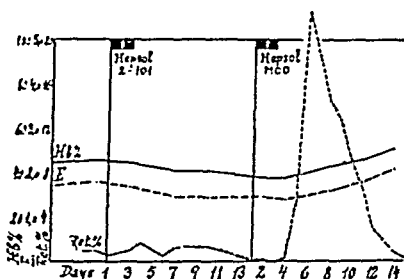
Fig. 5.

Recapitulation.   Liver extract (»Hepsol 2—101», 10 cm³ daily
for 2 days) from a swine, submitted to total resection of the fundus
with an observation period of 384 days, and treated for the last 132
days with a dried swine stomach preparation (Pylorin MCO) has
only a slight effect or none at all on the blood picture in 5 per-
nicious-anemic patients.

In one case (No. 1) where the morbid condition was not so
pronounced, the effect of this liver extract could not with certainty
be said to be inferior to that of the control preparations, which like-
wise had a rather poor effect. But in a pronounced case of the
disease (No. 2) the effect of this extract was considerably less than
that of the control preparation, and in the remaining three, likewise
pronounced, cases (Nos. 3, 4 and 5) this extract had no effect what-
ever, whereas the control preparation had a strong and typical effect.

Considerations concerning the Action of Pylorin as suggested by the
Present Experimental Results.

The experiment here reported has established that treatment
with Pylorin is able but in a slight degree to compensate the loss of
antipernicious-anemic principle in the liver, which is the constant

result of total resection of the fundus. Whether this loss is to be taken as an expression for complete abolition of the formation of this principle or merely a marked reduction in its formation, the supply of intrinsic factor has thus been unable to alter this condition essentially. While the intrinsic factor in the treatment of pernicious anemia brings about the formation of the antipernicious-anemic principle and the reappearance of this principle in the liver, the capacity of this factor for the exertion of a corresponding effect in swine is thus reduced when the fundus of the stomach has been eliminated.

From this it seems evident that there must be some relation of mutual dependence between the function of the fundus region and the intrinsic factor region. As to this mutual dependence two hypotheses will have to be taken into consideration.

One possibility is that the intrinsic factor acts on the fundus: in particular, this action might conceivably be of hormonal character (stimulating secretion and/or absorption).

The other possibility is that the fundus possesses certain properties, the presence of which is required for the functional manifestation of the intrinsic factor: either hormonal influence upon the amount of the factor in the »pyloric gland organ« (stimulation of the secretion) or liberation or digestion of a particular food element (extrinsic factor) necessary for the formation of the active principle in the intestinal canal.

That the intrinsic factor should be subject to regulation from the fundus is gainsaid by two facts: 1) administration of dried swine stomach from the fundus has previously shown to have no effect on the pernicious-anemic patients (Meulengracht); 2) removal of the fundus has apparently no influence on the intrinsic factor, although complete loss of the active principle in the liver is ascertained. The latter condition is evident not only from a previous therapeutic experiment (1941), but also from the following new experiment of the same kind.

A man, aged 53, suffering from typical pernicious anemia, for which he had received no treatment previously, was admitted to Dep. II of the Kommune Hospital (Reg. No. 499/1942). Here he was treated for 11 days with a daily dose of 20 g of a dried preparation of pylorus + duodenum + small intestine (»Pyloro-intestinin«, 1—105, MCO) from an experimental animal (S. 129) from which the fundus and cardia had been resected —

as mentioned in our preceding paper. This preparation produced the anti-pernicious-anemic effect presented graphically in Fig. 6.

In favour of the assumption that certain food elements have to be treated preliminarily by a fundus secretion it will be appropriate to cite the experiment originally reported by Castle (therapeutic effect in pernicious anemic patients from ingestion of meat predigested by normal human stomach juice) — only that, in this connection, particular stress is to be laid on the fundus secretion
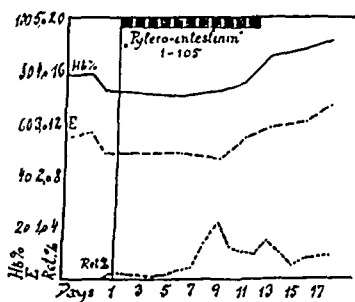
Fig. 6.

contained in the stomach juice. On the other hand, the necessity of a preliminary transformation of extrinsic factor in the fundus is gainsaid by the fact that ingestion of Pylorin in itself has a pronounced favorable effect in the achylic pernicious anemic patients, and also by the fact that parenteral administration of nicotinic acid together with cardiazone alone is sufficient for the formation of the active liver principle.

From the above considerations, then, at present we find it most likely that the intrinsic factor acts on the fundus. If this view through supplementary experiments proves to be correct, the Pylorin experiment here performed will further confirm our conception of the fundus as being of primarily decisive importance to the formation of the active liver principle. In this way, we have to admit, the role assigned to the intrinsic factor will be minor and quite different from the one now generally allotted to it.

Summary.

Liver extract (»Hepsol 2—101») is prepared from a swine submitted to total resection of the fundus, with an observation period of 12 ¾ months, and treated during the last 4 ½ months with dried swine stomach preparation, Pylorin MCO (about 20 g. daily).

The therapeutic effect of this extract was tried out on 5 pernicious anemic patients who then for control were treated with ordinary, standardized, liver extract (Hepsol MCO).

The experimental preparation produced only a slight blood reaction or none at all, whereas the control preparation gave a slight, moderate or strong reaction.

Thus treatment with Pylorin was not able to compensate the loss of antipernicious-anemic principle from the liver in pigs, which — according to our previous investigations — is a constant result of total resection of the fundus. In other words, the intrinsic factor is not able to bring about the formation of the antipernicious anemic principle when the fundus is eliminated. These findings appear to demonstrate the relation of mutual dependence between the function of the intrinsic factor region and the fundus region. The character of this functional relationship is discussed.

The Pylorin experiment here reported implies the possibility of additional confirmation of our view of the primarily decisive importance of the fundus to the formation of the active liver principle.

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Über die Wirkung des Bariums auf das Herz auf Grund zweier Vergiftungsfälle.

Von

MARTTI HIRVONEN, Hämeenlinna.
(Bei der Redaktion am 5. Juni 1944 eingegangen).

Das Barium in löslicher Form ist bekanntlich ein starkes Gift. Die kennzeichnenden Symptome der Bariumvergiftungen sind nach den pharmakologischen Lehrbüchern Übelkeit, grosses Schwächegefühl und Symptome seitens des Darmkanals, wie Erbrechen und Diarrhöe, sowie ausserdem Störungen der Herztätigkeit.

Da die Bariumsalze in löslicher Form sogar in kleinen Gaben nicht als Medikamente gebraucht werden und die Verwendung des löslichen Bariums auch sonst relativ beschränkt ist, sind die Bariumvergiftungen recht selten. Lösliches Bariumkarbonat ist jedoch ziemlich oft zur Verwendung gekommen und wird nach wie vor als Rattengift benutzt. Obgleich das Bariumkarbonat daher verhältnismässig leicht für die Ausrottung der Ratten zu haben ist, sind die Bariumvergiftungen doch sehr selten geblieben und sind eigentlich nur in einigen exzeptionellen Unglücksfällen vorgekommen, denn auch die Selbstmörder haben im allgemeinen kein Barium angewandt.

Unter diesen Umständen ist es leicht verständlich, dass die durch das Barium hervorgerufenen Vergiftungssymptome vorzugsweise auf Grund von Tierversuchen und nicht von klinischen Beobachtungen festgestellt sind. Dabei ist nachgewiesen worden, dass das Barium eine besondere Affinität zum Herzen hat. Auf
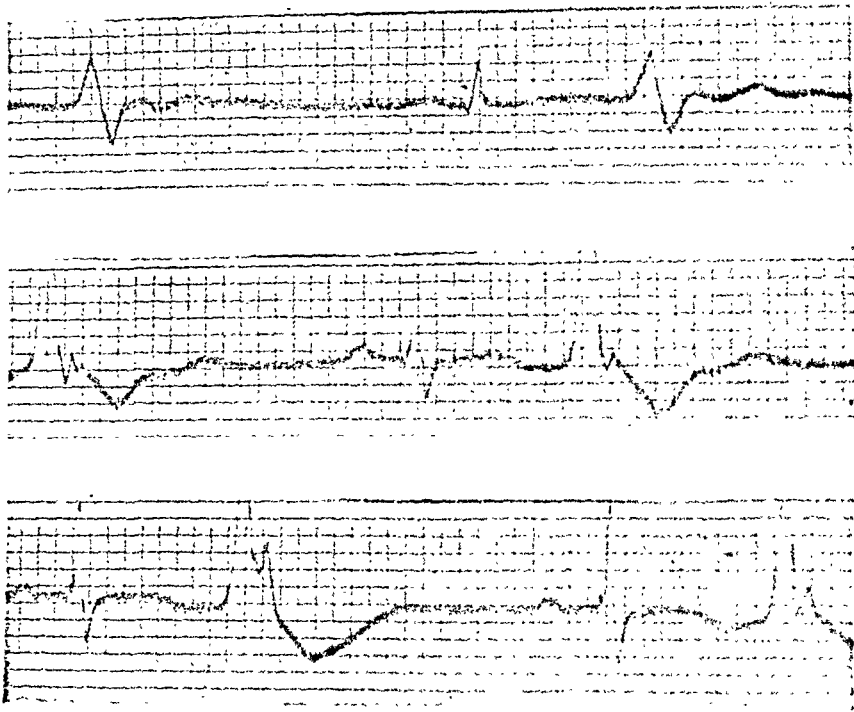
Fig. 1.

dieser Seltenheit der Bariumvergiftungen beruht es sicher auch, dass z. B. Hochrein nur das Arsenik, Wismut, Quecksilber und Blei nennt, aber das Barium unerwähnt lässt, wenn er von den toxischen Wirkungen der Schwermetalle auf den Herzmuskel spricht. Die toxischen Wirkungen des Bariums auf den Herzmuskel treten am deutlichsten als elektrokardiographische Veränderungen hervor. Die Veränderungen sind bei Tierversuchen, wie man konstatiert hat, in verschiedenen Fällen recht verschieden.

v. Werz hat experimentell die Wirkung des Bariums auf das Herz untersucht, indem er es unmittelbar auf die Oberfläche des Herzens wirken liess. Dabei fand er im Elektrokardiogramm ein schroff negatives T. Pearcy und Howard konstatierten ebenso experimentell beim Kaninchen ein negatives T und eine Verlängerung der QT-Zeit. Fogelson und Tschernogoroff sowie Agnoli und Bussa hinwieder haben eine Verkürzung von QT und eine monophasische Deformation des Kammer-Ekg, Zarafjan in der II. Ableitung eine Abflachung von R und T festgestellt.
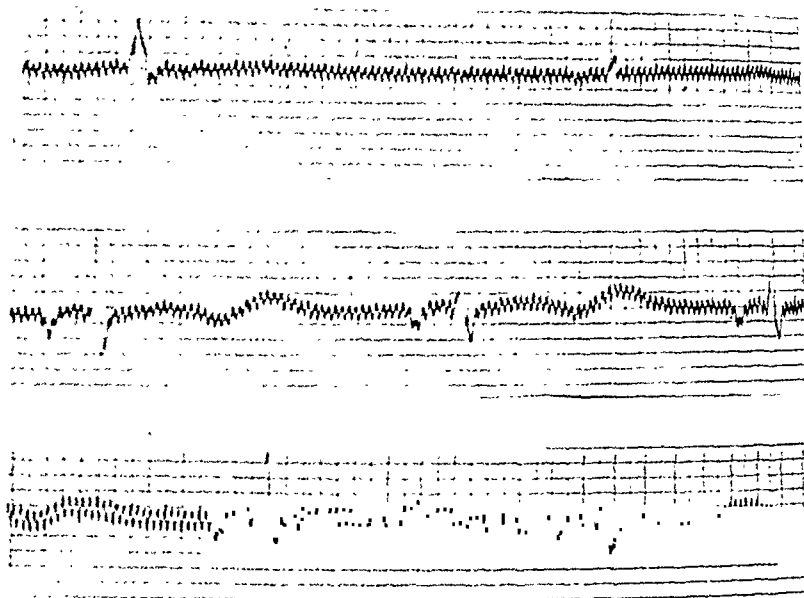
Fig. 2.

Nur Pariscenti hat klinische elektrokardiographische Unter-
suchungen auf Grund einer Bariumvergiftung veröffentlicht. Er
fand in diesem Fall eine starke Senkung der Strecke ST und Extra-
systolen, bei denen die QRS-Zeit über 0.25 Sek. betrug.

Bei den an einer Bariumvergiftung Gestorbenen ist am meisten
Barium im Blut, dem Herzen, den Lungen und besonders in chro-
nischen Fällen im Knochensystem angetroffen worden.

Wie wir alle wissen, wird Barium in Form des unlöslichen
Bariumsulfats allgemein als Kontrastmittel bei Röntgenunter-
suchungen des Magens und Darmkanals gebraucht. Da das unlös-
liche Bariumsulfat durchaus ungefährlich ist, sind wenigstens bei
uns in Finnland früher nie Bariumvergiftungen im Zusammenhang
mit Röntgenuntersuchungen festgestellt worden. Vor kurzem hatte
ich jedoch zwei bei solchen Untersuchungen angetroffene Fälle
von Bariumvergiftung zu behandeln, die so entstanden waren, dass
das Bariumpulver, aus dem das den Patienten gegebene Kontrast-
mittel angefertigt war, aus einer unbekannten Ursache als Ver-
unreinigung eine sehr beträchtliche Menge lösliche Bariumsalze,
hauptsächlich Bariumkarbonat, enthielt, obgleich es ein von einer
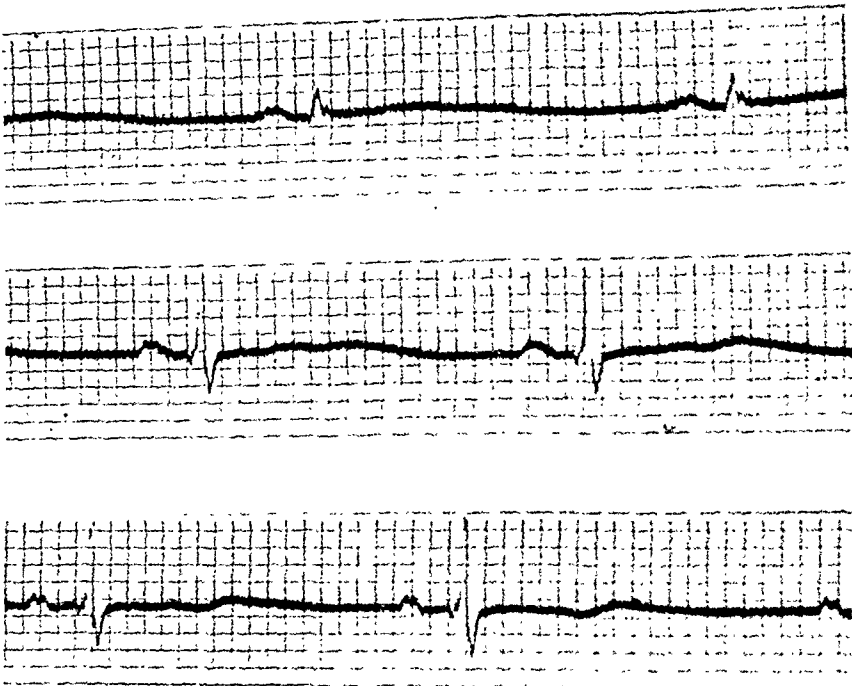
Fig. 3.

bekannten ausländischen Fabrik hergestelltes und garantiertes Barium sulfuricum purissimum pro röntgen-Präparat war. Allem Anschein nach war die Vrunreinigung auf die eine oder andere Weise hinterher in den Kontrastmittelbeutel gekommen, denn das als Verunreinigung nachgewiesene Bariumkarbonat war dem Kontrastmittelpulver sehr ungleichmässig beigemischt.

Wegen der grossen Seltenheit der Fälle habe ich es angebracht gefunden, diese beiden von mir behandelten Fälle, deren hauptsächliche Symptome Herzsymptome waren, mitzuteilen.

Die beiden Patienten waren junge Männer, die dyspeptische Beschwerden hatten, und es war beschlossen worden, an ihnen hauptsächlich zwecks Ausschliessung der Möglichkeit von Ulkus eine Röntgenuntersuchung des Magens auszuführen. Die Röntgenuntersuchung fand zwischen 9 und 10 Uhr morgens statt, nachdem die Patienten seit dem vorhergehenden Abend weder etwas gegesssen noch getrunken und auch keine Medikamente zu sich genommen hatten. Von den Bauchbeschwerden abgesehen, waren beide gesunde Männer und fühlten sich beide wohl, als sie zu der Unter-
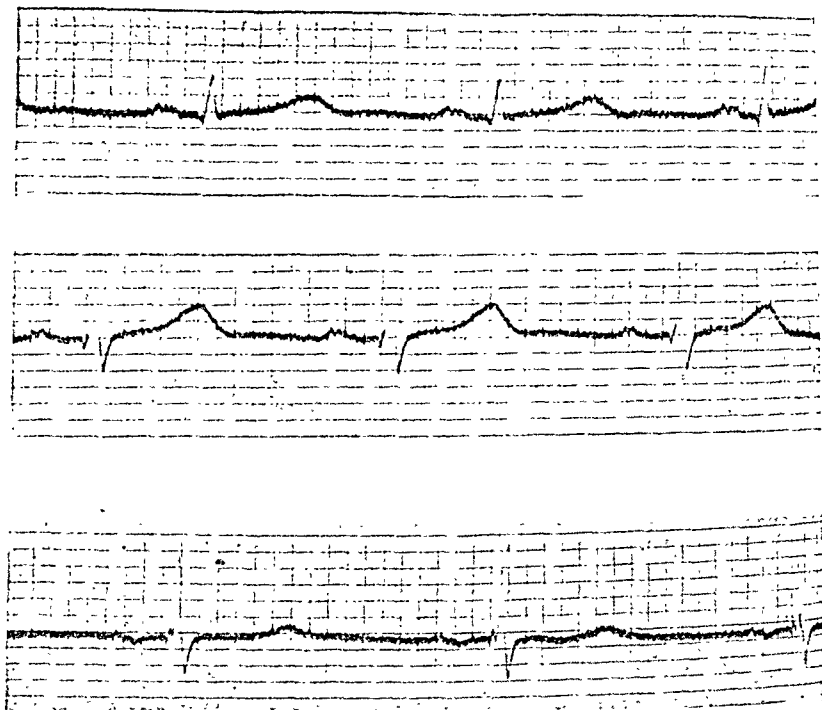
Fig. 4.

suchung gingen. Von der Röntgenabteilung auf die Krankenabtei-
lung zurückgekehrt, begannen beide über Übelkeit und Schwäche
zu klagen.. Um 12 Uhr erbrachen sich beide reichlich und hatten
beide Diarrhöe. Um 14 Uhr hatte sich ihr Zustand dermassen ver-
schlechtert, dass der Verfasser auf die Abteilung alarmiert wurde.

   Da konstatierte ich sofort, dass eine schwere akute Vergiftung
vorlag, und da die Patienten an dem Tage noch nichts anderes
als Bariumbrei genossen hatten, richtete sich der Verdacht sogleich
auf eine Bariumvergiftung. Der Verdacht wurde in hohem Masse
dadurch verstärkt, dass die Herztätigkeit beider Patienten erheblich
gestört war. Beide hatten einen weichen und der eine überdies einen
unregelmässigen, der eine einen gewöhnlich grossen, der andere
einen kleinen Puls. Der Schall und die Stärke der Herztöne waren
normal. Bei dem einen war jeder zweite Schlag ein überzähliger.
Die an beiden ausgeführten elektrokardiographischen Untersuchun-
gen gebe ich weiter unten gleichzeitig wieder.
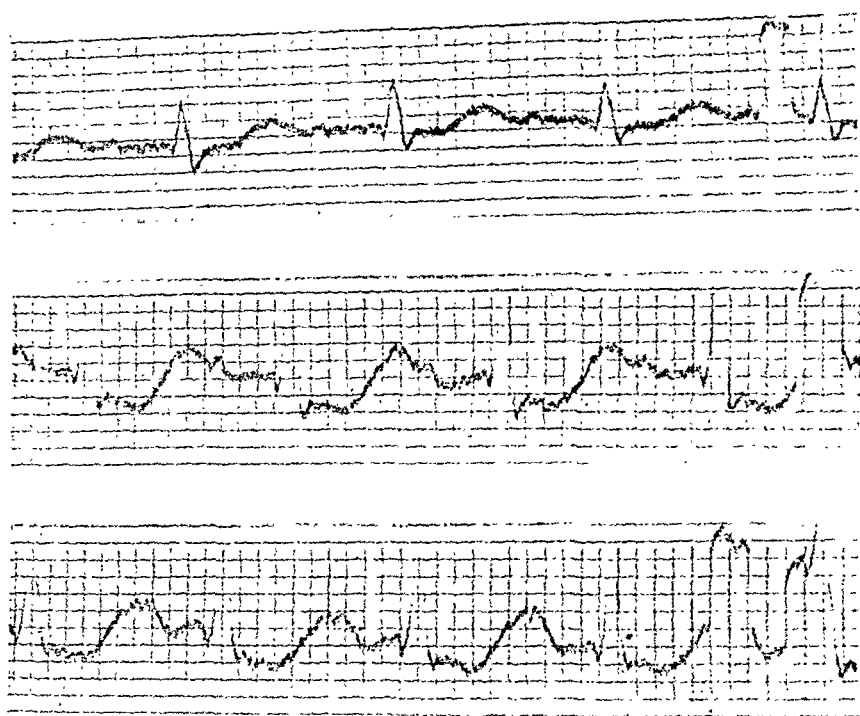
Fig. 5.

Als Therapie wurden das Gegengift des Bariums, Magnesium-sulfat, das jedoch beide ausbrachen, sowie Darmspülungen mit kohlenhaltigem Spülwasser angewandt. Ausserdem bekamen beide Herzmedikamente. Mit dieser Therapie erholte sich das eine Opfer der Vergiftung auch bis zum Abend von den schlimmsten Vergiftungssymptomen und erreichte eine so gute Verfassung, dass es am Abend sogar Speise zu sich nehmen konnte. Am Abend traten bei ihm keine Extrasystolen mehr auf. Die Genesung schritt dann allmählich so weit fort, dass das Befinden des Patienten 6 Tage nach der Vergiftung recht gut und in der Herztätigkeit klinisch oder elektrokardiographisch nichts Pathologisches fest-zustellen war.

Der Zustand des anderen Vergifteten verschlechterte sich dagegen von Stunde zu Stunde trotz der Therapie. Seine Atmung wurde allmählich immer oberflächlicher, und es begann bei ihm Zyanose aufzutreten. Sein Puls war andauernd regelmässig und wurde im Lauf des Nachmittags grösser, nachdem er früher sehr klein gewesen war. Wegen offensichtlichen Sauerstoffmangels
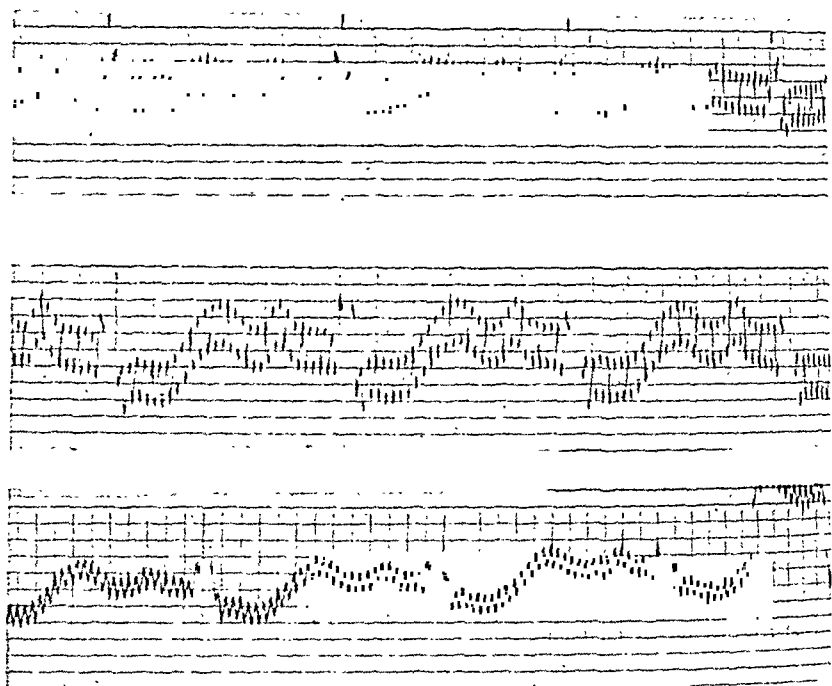
Fig. 6.

versuchte ich dem Patienten zuerst künstliche Atmung zu geben, aber diese schien ihn nur anzustrengen, und man sah keinen Nutzen davon. Deswegen ging ich dazu über, Sauerstoff durch eine Nasenkanüle zu geben, aber auch das half nichts, sondern um 23.25 trat unter deutlichen Erstickungssymptomen der Exitus letalis ein.

Bei der am folgenden Tage ausgeführten Obduktion stellte ich fest, dass die Lippen und die anderen sichtbaren Schleimhäute bleich, die Pupillen rund und maximal erweitert waren. Blutgefässe der Pia mater ziemlich reichlich mit dunkelrotem Blut gefüllt. Schnittfläche des Gehirns mehr als gewöhnlich blutpunktiert. Schleimhaut der Luftröhre dunkelrot. Perikard in grösserem Umfang als gewöhnlich sichtbar. Auf der Oberfläche beider Lungen recht zahlreich stecknadelkopfgrosse dunkelblaue Flecke. In der Magenschleimhaut deutliche Blutergüsse. Schleimhaut des Dünndarms dunkel blaurot, ebenso Schleimhaut des Dickdarms. Struktur der Leber etwas undeutlicher als gewöhnlich. Sonst war bei der Obduktion nichts von der Norm Abweichendes zu bemerken.

Bei der chemischen Untersuchung wurden in ziemlich grosser Menge Bariumionen im Blut und lösliche Bariumsalze im Darminhalt gefunden.

Bei den elektrokardiographischen Untersuchungen konnte eine starke Giftwirkung des Bariums auf das Herz festgestellt werden. In dem Fall, der von der Vergiftung genas (Fall 1), wurden elektrokardiographische Untersuchungen so lange ausgeführt, bis alle pathologischen Zeichen verschwanden, was 6 Tage nach der Vergiftung geschah. Von dem letal ausgegangenen Vergiftungsfall (Fall 2) konnten vor dem Tode 2 Elektrokardiogramme genommen werden. Bei den elektrokardiographischen Untersuchungen wurden folgende Beobachtungen gemacht.

Fall 1. EKG Nr. 1. 3 Stunden nach der Vergiftung. Abbildung 1. Extrasystolische Allorrhythmie des Bigeminietypus. Pulsfrequenz 85/Min. Bei den Normalschlägen PQ-Zeit 0.15 Sek. und QRS-Zeit 0.08 Sek. T_I sehr niedrig, fast isoelektrisch, T_{II} niedrig und T_{III} fast isoelektrisch. Relative QT-Zeit nach Lepeschkin 114 %. Die Extrasystolen sind ventrikulär und kommen regelmässig nach der T-Welle. Sie sind in der I. und II. Ableitung untereinander von gleicher Form, in der III. Ableitung treten kleine Unterschiede in der Form der verschiedenen Extrasystolen auf.

EKG Nr. 2. 10 Stunden nach der Vergiftung. Abbildung 2. Langsamer Sinusrhythmus oder Nodalrhythmus. Pulsfrequenz 55/Min., P_I fehlt, P_{II} und P_{III} negativ. QRS_I bei einigen Schlägen von gewöhnlicher Grösse, meist ganz klein. Die grösseren von diesen dürften Extrasystolen sein können. PQ-Zeit 0.15 Sek. QRS-Zeit 0.06 Sek. T_I schwach positiv, T_{II} und T_{III} negativ. Deutliche U-Welle in allen Ableitungen. Relative QT-Zeit nach Lepeschkin 112 %.

EKG Nr. 3. 24 Stunden nach der Vergiftung. Abbildung. 3. Langsamer Sinusrhythmus. Pulsfrequenz 52/Min. P_I, P_{II} und P_{III} positiv, P_{II} und P_{III} deutlich zweigipflig. PQ-Zeit 0.15 Sek. QRS-Zeit 0.06 Sek. In QRS_I eine Knotenbildung. T_I ganz schwach positiv, T_{II} undeutlich, T_{III} negativ. In der I. Ableitung undeutliche, in der II. und III. Ableitung deutliche U-Welle. Relative QT-Zeit nach Lepeschkin 96 %.

EKG Nr. 4. 6 Tage nach der Vergiftung. Abbildung 4. Sinusrhythmus. Pulsfrequenz 73 Min. P_I, P_{II} und P_{III} positiv, P_{III} sehr klein. PQ-Zeit 0.15 Sek. QRS-Zeit 0.07 Sek. T_I, T_{II} und T_{III} deutlich positiv. Eine U-Welle kommt nicht mehr zum Vorschein. Relative QT-Zeit nach Lepeschkin 113 %.

Fall 2. EKG Nr. 1. 5 Stunden nach der Vergiftung. Abbildung 5. Sinusrhythmus. Pulsfrequenz 101/Min. P_I, P_{II} und P_{III} positiv. PQ-Zeit 0.20 Sek. QRS-Zeit 0.10 Sek. T_I, T_{II} und T_{III} positiv. ST_I etwas, ST_{II} und ST_{III} ausserordentlich stark unterhalb der isoelektrischen Linie. Relative QT-Zeit nach Lepeschkin 147 %.

EKG Nr. 2. 10 Stunden nach der Vergiftung. Abbildung 6. In der Abbildung zahlreiche elektrische Störungen. Sinusrhythmus. Pulsfrequenz 95/Min. P_I, P_{II} und P_{III} positiv. PQ-Zeit 0.20 Sek. QRS-Zeit 0.08 Sek. T_I, T_{II} und T_{III} positiv. ST_I, ST_{II} und ST_{III} deutlich unterhalb der isoelektrischen Linie. Relative QT-Zeit nach Lepeschkin 141 %.

Besprechung der Ergebnisse.

Nach den verschiedenartigen Symptomen und dem verschiedenartigen Verlauf der Krankheit ist es augenscheinlich, dass der eine Patient eine bedeutend grössere Menge lösliches Bariumsalz bekommen hatte als der andere. Die chemische Untersuchung des Bariumpulvers zeigte auch, dass es sich offenbar so verhielt, denn von dem als Verunreinigung aufgetretenen löslichen Bariumkarbonat fand sich in den einen Schichten des Pulverbeutels reichlich, in den anderen wenig oder kaum etwas.

Die elektrokardiographischen Veränderungen des leichten Vergiftungsfalls entsprechen am ehesten dem Bild, das die Myokardschädigungen geben. Die wichtigsten Veränderungen waren anfangs zahlreiche Extrasystolen, später langsamer Sinusrhythmus oder Nodalrhythmus, Abflachung der T-Welle und Auftreten einer U-Welle. Leitungsstörungen fanden sich nicht. Die QRS-Zeit war im Gegenteil zuweilen vielleicht sogar etwas kürzer als gewöhnlich. Die relative QT-Zeit war andauernd normal. Eine Abflachung der T-Welle hatte Zarafjan in den von ihm ausgeführten Tierversuchen festgestellt, und in Pariscenti's Versuch kamen Extrasystolen vor wie in diesem meinem leichten Fall.

In dem schweren Vergiftungsfall wurden dagegen eine leichte Leitungsstörung — sowohl die PQ- als die QRS-Zeit waren wahrscheinlich etwas verlängert —, eine starke auf Koronarinsuffizienz hinweisende Erniedrigung der Strecke ST und eine Verlängerung der QT-Zeit beobachtet. Das Ergebnis entspricht mithin teilweise den von Pearcy und Howard experimentell an Kaninchen ausgeführten Untersuchungen, in denen die QT-Zeit auch verlängert war. Fogelson und Tschernogoroff sowie Agnoli und Bussa hatten bei ihren Tierversuchen konstatiert, dass sich die QT-Zeit umgekehrt verkürzte. Mit dem Fall von Pariscenti war die starke Erniedrigung der Strecke ST gemeinsam.

Zusammenfassung.

In der Arbeit sind zwei charakteristische Bariumvergiftungsfälle mitgeteilt, von denen der eine im Lauf von 6 Tagen vollständig genas, der andere dagegen 14 Stunden nach der Vergiftung starb. Bei der Obduktion und der sich daran anschliessenden chemischen Untersuchung konnte mit Sicherheit festgestellt werden, dass eine Bariumvergiftung vorlag.

· Besondere Aufmerksamkeit wurde der das Herz betreffenden Wirkung des Bariums auf Grund elektrokardiographischer Untersuchungen zugewandt. Es wurden folgende Beobachtungen gemacht:

In dem leichten Vergiftungsfall trat anfangs extrasystolische Allorrhythmie des Bigeminietypus auf, die sich schon 10 Stunden nach der Vergiftung in langsamen Sinusrhythmus oder in Nodalrhythmus verwandelt hatte, denn die P-Welle war da in der II. und III. Ableitung negativ, während die PQ-Zeit andauernd normal war. Die QRS-Zeit war bei einigen Untersuchungen vielleicht ein wenig verkürzt. In QRS_I wurden einmal Knoten konstatiert. Die T-Welle war in allen Ableitungen sehr flach. Die relative QT-Zeit war andauernd normal. Eine deutliche U-Welle trat in allen Ableitungen auf. Alle diese Veränderungen waren 6 Tage nach der Vergiftung verschwunden.

In dem schweren Vergiftungsfall bestand fortwährend Sinusrhythmus. Die P-Welle war während der ganzen Zeit in allen Ableitungen positiv. Die PQ-Zeit war wahrscheinlich etwas verlängert, ebenso die QRS-Zeit im Anfang. Die T-Welle war in allen Ableitungen positiv. Die Strecke ST war fortwährend stark erniedrigt, und die relative QT-Zeit war immer deutlich verlängert.

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On Mixed Forms of Pyelonephritis and Diffuse Glomerulonephritis.

By

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After Longcope's detailed description of 31 cases of pyelonephritic contracted kidney had been published in 1937, special notice was taken of the symptom complexes that are characterized *by the clinical picture of a diffuse glomerulonephritis, combined with infected urine.* This syndrome is not uncommon. A number of fairly well confined diseases of clinical importance are concealed therein. The following report is based upon cases from the Medical Clinic III at Helsingfors.

Acute cases.

The acute pyelonephritis may probably arise in three different ways: from haematogene infection, from infection arising from the urinal bladder, and from lymphogene infection from the colon and urogenital organs. Such releasing and cooperativ efacts which cause the kidneys to become susceptible to infection in some way are very important. Whether correctly or not — all such factors that cause retention of urine are mentioned in the first place, for example pregnancy, paralysis of the bladder, prostatic hypertrophy, stones, etc. Practical experience shows that chills play a great rôle. Relapses, caused by other diseases that influence the general state of immunity are often noticed. *Angina tonsillaris*

may be mentioned among these. The defloration-»pyelite» and acute attacks during menstruation are well known.

Among 300 cases of pyelonephritis in the Medical Clinic III the following disease releasing facts may be determined:

Paralysis of the bladder	5
Salpingo oophoritis	6
Acute infection of respiratory organs	6
Chills	13
Pregnancy	18
Angina tonsillaris	80
Unknown	172
	Total 300

5 cases suffered from paralysis of the bladder arisen from various causes. In 18 cases pregnancy pyelonephritis occurred, and in 6 cases the symptoms had appeared in connection with salpingo oophoritis. In 172 cases, i.e. in more than half the number of the cases, the anamnesis did not state any disposing or releasing facts. 13 patients had stated that the symptoms appeared directly after a chill. *In the case of 80 patients the anamnesis stated that the disease was connected with tonsillar angina, and in 6 cases a connection with an infection in the respiratory organs. Of these 80 cases 5 had fallen ill with pyelonephritis at the same time or a few days after the angina, 31 had sickened after a latent healthy postanginous period of 1 to 4 weeks, and 4 cases had not sickened until 5 to 8 weeks after the angina.* The remaining 40 cases had suffered several times from angina but the period that had elapsed between the bouts of angina and the pyelonephritis or the attacks of pyelonephritis was not clear.

This report does not claim to be exact. It is, however, remarkable that the anamnesis of nearly one third of the cases includes one or more cases of angina or infection in the respiratory organs, and that *in 12 per cent the relationship between the angina and the pyelonephritis was the same as it generally is between angina and diffuse glomerulonephritis, i.e. the pyelonephritis did not become acute until the elapse of a latent postanginous period of 1 to 4 weeks.*

In glomerulonephritis the immune biological adaption takes place during the latent post anginous period. In special circumstances it results in a condition of super-sensitiveness, in an allergy.

The acute glomerulonephritis represents the allergic reaction that is released in the super-sensitive organism by the allergen. It consists of streptococci, or their products, that have caused the angina.

The pyelonephritis is not caused, as known, by streptococci but in the majority of cases (70—80 per cent) by bacterium coli. (In all my cases a bacterium coli culture or not closely determined Gram-negative staves had been obtained from the urine.) Characteristic of the pyelonephritis is as well the mattery bacterial inflammation, but the glomerulonephritis kidneys are sterile. The relationship between the angina and the pyelonephritis must, on this account, be different to that of the angina and the glomerulonephritis.

Pathology may give an information of what the causal nexus may be. If an allergen sensitizes the organism it may happen that the predisposition to inflammation of the organism is increased also in regard to other factors that produce inflammation. Moro & Keller have called it *parallergy*. The connection between angina and pyelonephritis is based upon such a parallergy. *The immune-bacteriologic adaption created by the infection of streptococci causes the organism to become still more susceptible to infection of other bacteria.*

Angina thus seems to prepare the kidneys for an infection of coli bacteria. It is probable that a period of 1—4 weeks are required for this purpose, or, as long time as required for causing the sensibility for a glomerulonephritis to take place. In such circumstances it lies close at hand to suppose that *after an angina, the patient might fall ill simultaneously with a pyelonephritis and a diffuse glomerulonephritis.*

Such cases do occur. 3 cases of this kind will be given below.

Journ. No. 1651/1935. Married woman. 21 years. Three weeks ago *sore throat* and temperature for 2 days. 10 days later very swollen face, arms and legs, difficulty in breathing and palpitation of the heart. — *State:* Large *oedema* of face and legs. Complexion pale. Temperature 38.3. Difficulty in breathing when in motion. Heart and lungs stethoscopically nothing noteable. Liver not enlarged. Blood prussure 150/110 Hg. — *Urine:* Macroscopically cloudy, brown, proteins 4 pro mille specific gravity 1026. Numerous erythrocytes in sediment. Fair amount of leucocytes and hyaline-granulated — and cellcasts. Bacterium coli plentifully. *Blood:* Non-protein nitrogene 38.7 mg per cent. Indikan —. Sed. rate 32 mm. — *Course:* After a 4-day period of a diureses 200—400 cm³, the volume of urine

increased, the quantity of proteins decreased, oedema disappeared and the blood pressure fell successively to 90/70 mm Hg. The urine became sterile after hexacamphine injections but still 2 ½ months later a slight proteinuria and a very little sediment remained. Concentration spec. grav. 1029. S. R. remained raised.

Journ. No 2443/1936. Married woman. 32 years. Angina tonsillaris repeatedly. 2.10. again angina tonsillaris and 16.10. otitis. A few days later the volume of urine decreased and the patient passed only small quantities with *great tenesmes*. Tired, headache, pains in loin. State 23/10: Temperature 37.8. No oedema. Pale. Difficulty in breathing when in motion. Lungs and heart stethoscopically nothing noteable. Liver not enlarged. *Blood pressure:* 165/110 mm Hg. *Urine:* Macroscopically cloudy, dark, proteins 1 pro mille sp.g. 1021. In sediment moderate amount of erythrocytes, hyaline and granulated casts, numerous leucocytes and bacterium coli. *Non-protein nitrogen of blood:* 37.8 mg per cent. Indikan —. S.R. 32 mm. *Course:* In the beginning urine sparingly, after one week an increase. Amount of proteins reduced by half within 10 days and disappeared altogether in three weeks. At the same time there was a fall in the blood pressure but it did not reach 120/90 mm Hg. until 8 weeks later. Infection of coli resisted all treatment. When discharged, after 9 weeks in hospital, bacterium coli still plentiful, leucocytes sparingly, and a few casts. Pyelograms showed normal pelvis but a somewhat retarded excretion of dye. Concentration: spec. g. 1026.

Journ. No 460/1937. Married woman. 30 years. 10 days ago *angina tonsillaris*. Now, for some days, swollen face, headache. *State:* Oedema of face, pale. Temp. 38.5. Heart and lungs stethoscopically nothing noteable. Liver not enlarged. *Blood pressure:* 150/100 mm Hg. *Urine:* Sparingly, dark, cloudy, proteins 0.5 pro mille spec. g. 1030. In sediment erythrocytes plentifully, leucocytes and bacterium coli, granulated and hyaline casts sparingly. *Non-protein nitrogen of blood:* Not examined. S.R. 20 mm. *Course:* Proteinuria disappeared in 10 days and the blood pressure fell to 90/70 mm Hg. At the same time the volume of urine increased to 2,000 cm and the oedema disappeared. After injections of hexacamphine the urine became sterile. Free from symptoms in 5 weeks.

These three patients thus showed symptoms of diffuse glomerulo-nephritis as well as of pyelonephritis after having suffered from angina though the combination of symptoms differ somewhat. They had oedema, hypertension, proteinuria and »nephritic» sediment with urine infected with bacterium coli, pains in the back, urinal tenesmes and temperature. One of them became quite free from symptoms, in one case a slight proteinuria and a sparing sediment with sterile urine remained. In the last mentioned case the urine became free from proteins but still contained bacterium coli and

some sediment. In all of these cases the elevated blood pressure fell to normal values.

Besides these three cases there are 7 cases in which the patients, after having suffered from angina, were taken ill 1 to 4 weeks later with *acute febrile pyelonephritis but some solitary symptoms suggesting glomerulonephritis* appeared as well. 5 of them suffered from oedema of the face and 2 of these patients had also *nephritic sediments* with erythrocytes in abundance and casts and proteinuria up to 2 pro mille. 2 patients suffered from hypertension, one of them 180/110, the other one 155/95 mm Hg. The blood pressure fell in both cases when the pyelonephritis disappeared.

We may, of course, discuss, whether we have a right to consider the hypertension and the oedema in these 7 cases as signs of glomerulonephritis. In support of such an interpretation we may state that Volhard, among others, has pointed out and stressed the importance of the fact that elevated blood pressure, passing oedema and proteinuries which must be taken as incomplete glomerulonephritis are noticed fairly often after an angina. They are often not diagnosed and may, perhaps, on this account, give rise to stealthy chronic glomerulonephritis of seemingly obscure etiogy.

Chronic cases.

The chronic bilateral pyelonephritis or pyelonephritic contracted kidney has probably very often developed from an acute pyelonephritis but in many cases the anamnesis does not give any information that might be interpreted in this direction. The course may be, in the beginning — during several years — very poor in symptoms: sometimes there are no urination troubles and the only symptoms may be transitory pyuries and coliuries. In other cases the disease may be characterized by frequent cystic or pyelitic troubles or acute attacks of pyelonephritis. The disease is gradually transformed into a state of renal insufficiency and a slowly progressing uremia develops. The clinical picture of this disease does not differ from uremia in chronic diffuse, glomerulonephritis. The specific gravity of the urine is fixed at a low value, the non-protein nitrogen of the blood increases, the patient becomes anemic, loses weight, vomits and dies in coma. In some cases, but not in all, a *hypertension develops that may have very high values* and that has the

character of a malignant hypertension with paleness, changes in
the eye-grounds and cerebral symptoms. In these cases myocardial
changes and cardiac insufficiency may be noticed as well, and death
may be caused by hypertension.

The urine contains small quantities of proteins (from traces up
to some pro mille), generally a fair amount of leucocytes, and
erythrocytes and casts sparingly. The urine is often macroscopically
clouded with bacterium coli but sometimes the bacteria can only be
traced by culture.

In more advanced cases the pyelography discloses deform-
ations, flattenings and reductions of the pelvis or hydronephrosis.
The ureters may be expanded in their entire length or irregularly.

An inflammatory reaction in the interstitial tissue, periglome-
rular fibrosis, and within the tubuli, casts surrounded by atrophic
epitel are seen pathologic-anatomically (Longcope, Weiss & Parker).
The process leads to a gradual destruction and replacement of the
kidney tissue by inflammatory tissue and contraction of the scars.
Vasculary changes are noticed especially in cases of long duration
which, according to Weiss & Parker are often represented by a
special type of productive endarteritis and necroticing arteriolitis.
The luminas of the vessels may be highly narrowed.

As an example of cases with a fair lack of symptoms in the
course, the following may be given:

Journ. No 2210/1937. Unmarried woman. 59 years. Has been »healthy
all her life» until in June 1935 when she developed a temperature, felt urinal
tenesmes and vomited. An acute febrile pyelonephritis was diagnosed at
the hospital. Heart and lungs nothing noteable. The urine contained traces
of protein, bacterium coli, leucocytes and erythrocytes plentifully, no
casts. Blood pressure 110/70 mm Hg. S.R. 114 mm. Concentration power
of kidneys good. The urine did not become sterile. — The patient then
felt well and was at work until the beginning of July 1937 when she began
to be troubled by headaches, vertigo, tiredness, loss of appetite, and at
times vomiting. Lost weight heavily. No urinating troubles. Admitted into
hospital 30/7 1937 with fully developed uremia. Somnolent, non-protein
nitrogen of blood: 154 mg per cent, indikan +, volume of urine 200—800
cm³/day with a specific gravity fixed at 1008. The blood pressure had
risen to 180/120 mm Hg. The urine contained about 1 pro mille protein
and bacterium coli, leucocytes and erythrocytes plentifully. The heart
showed myocardial changes but was not insufficient. No eye-ground chan-
ges. Anemia of 68 per cent Sahli and 3.39 million erythrocytes. S.R. 115
mm. Died in uremic coma 10 days later.

The clinical picture may in many cases resemble the clinical picture of chronic diffuse glomerulonephritis. *The only difference may be the presence of bacterium coli in the urine.*

From many quarters — among others Sholl & Harrison — *a demand has now been put up that cases of diffuse glomerulonephritis shall not be accepted as such, before the possibility of a bilateral chronic pyelonephritis has been excluded by repeated negative culture of urine.*

This demand is, however, carried too far, as there are, in reality, mixed forms of chronic diffuse glomerulonephritis and chronic bilateral pyelonephritis. Longcope, for instance, discovered in three cases of contracted kidney a microscopic picture of a chronic diffuse glomerulonephritis besides the pathologic-anatomical changes that are characteristic of this disease. It is obvious that such cases cause insurmountable diagnostical difficulties.

Some examples from the Medical Clinic III may be cited:

Journ. No 1046/1938. Unmarried woman. 43 years. Never had any urination troubles. No anamnestic information suggesting pyelonephritis. For three years she has suffered from headache and for one year of backache. Admitted into hospital for these troubles. *State:* General condition good, rather pale and thin. Lungs, nothing noteable. Left side of heart enlarged, no symptoms of heart failure. *Blood pressure:* 195/125 mm Hg. *Urine:* Cloudy, pale. Proteinuria 10 pro mille, numerous leucocytes in sediment, erythrocytes moderately, a few casts, and bacterium coli in abundance. Concentration and dilution tests reveal a hypostenuria between 1003 and 1013. Non-protein nitrogen of blood: 43 mg per cent, indikan $+$. S. R. 26 mm Hgb 70 per cent. Sahli, erythrocytes 3.28 millions. The pyelogram shows normally shaped pelvis and ureters but a retarded and reduced excretion. From both kidneys urine containing bacterium coli. *Course:* Treated with hexamine and almond-acid. Non-protein nitrogen of blood not reduced and functions of kidneys remained unchanged. The urine did not become sterile, sediment unchanged, proteinuria 2—3 pro mille.

Journ. No 500/1935. Male. 43 years. In 1918, after the »Spanish influenza» both legs were paralysed and the patient could neither pass urine nor move his bowels. One year in hospital (Med. Clin. I.) during which time the paralysis was cured and he was quite well. In 1931 attended for inflammation of the bladder for 3 months. Then again quite recovered but inclined to urinate more often than usual. In February 1935 he began to be troubled by shortness of breath, severe cough, was very tired and came to the hospital as he noticed that his face, arms and legs were swelling. *State:* Face deformed from oedema, moderate oedema in legs and arms. Complexion pale. No auscultatory changes, irritated by cough. Heart not enlarged. Liver not swollen. *Blood pressure:* 170/100 mm Hg. *Urine:* Pale, cloudy, proteinuria 2—3 pro mille, numerous leucocytes in

sediment, erythrocytes, hyaline and granulated casts moderate, abundance of bacteria. Concentration and dilution show a hypertension between 1004 and 1014. *Non-protein nitrogen of blood:* 46.8 mg per cent, indikan +. Hgb. 80 per cent. Sahli, erythrocytes 3.54 millions. S.R. 8 mm. Eye-grounds nothing noteable. *Course:* Diet and treatment with various urine disinfectants. The oedema disappeared. The blood pressure fell to 140/90. Non-protein nitrogen of blood and power of concentration in the kidneys unchanged. Proteinuria remained between 2—3 pro mille, the sedimentation rate decreased but the bacteria did not 'disappear. Subjectively recovered.

The first case refers to a woman who lacks signs of pyelonephritis in her anamnesis and who shows hypertension, proteinuria in a high degree, and renal insufficiency. She has a coli-uria, but no change in the pelvis of the kidneys are indicated roentgenologically. There may be a question of pyelonephritic contracted kidney or a mixed form of glomerulonephritis and pyelonephritis. The second case refers to a man who had had a (ascending?) pyelonephritis. He fell ill later with oedema, hypertension, proteinuria, nephritic sedimentation and infected urine and renal insufficiency. In the clinical picture the oedema indicates principally a glomerulonephritic component.

How do these chronic mixed forms arise?

There is a possibility that they *originate in the acute mixed forms.* As the chronic pyelonephritis may develop out of unhealed acute pyelonephritis or from relapses of pyelonephritis, and the chronic glomerulonephritis from acute glomerulonephritis, the chronic mixed forms must also be able to develop from acute forms. Probably the slight abortive cases, poor of symptoms, may play a rôle of no little importance. Because they are not diagnosed, or at least not correctly interpreted, they do not receive the treatment that might prevent a transition into a chronic state. Clinical and pathological-anatomical studies should give an answer to these questions.

It is also possible that the two diseases have not arisen simultaneously. The glomerulonephritis may have been the primary disease. Perhaps the glomerulonephritis kidneys are more susceptible to haematogene infections of bacteria than healthy kidneys are. As an example of cases, in which such a development seems to be indicated, the following clinical reports of three patients may be given:

Journ. No 2019/1937. Unmarried woman. 30 years. In 1932 treated in the Med. Clin. I for acute diffuse glomerulonephritis. Since then urination troubles in the form of burnings and tenesmes. Admitted into the Med. Clin. III in 1937 with an acute febrile pyelonephritis lasting three weeks. The urine became free from proteins but not from bacteria (Bacterium coli).

Journ. No 1082/1939. Male. 32 years. Treated in the Med. Clin. I, in 1937, for acute diffuse glomerulonephritis. In 1934 blood pressure 130/80, in urine traces of proteins but no bacteria. In 1939 blood pressure 125/90 in urine, proteins 1 pro mille, numerous leucocytes, scarcity of erythrocytes, some casts, and enterococci plentifully. The urine did not become free from proteins nor from bacteria.

Journ. No 1471/1934. Married woman. 38 years. In 1928 nephritis with high blood pressure. In 1932 blood pressure normal. In 1934 admitted with acute febrile pyelonephritis. In urine 1 pro mille protein, pyuria and bacterium coli plentifully. The proteinuria reduced to traces. The urine did not become sterile. Blood pressure 130/95.

These examples might be added to. Among 30 cases that showed symptoms of pyelonephritis as well as of diffuse glomerulonephritis 8 cases may be interpreted in this forementioned way.

If there is a reason to believe that the pyelonephritis has been the primary and glomerulonephritis the secondary, two more or less theoretical foundations for an explanation may be considered.

It is possible that an infection of bacterium coli might cause the kidneys to be more susceptible to a streptococc-glomerulonephritis. On the other hand we may imagine that the coli bacteria might sensitize the kidney tissues. A continued infection might lead to an allergic reaction in which the coli bacteria themselves would act as an antigen. Practical evidence of this theory is lacking.

The second possibility lies in the fact that the changes in the bloodvessels — sclerosis of the bloodvessels — in advanced cases of pyelonephritis with hypertension might, in some way, produce glomerulonephritis. There is no evident proof for this thought either, but there is a point in one of the cases described by Stewart that we may attach importance to. In a hypertonic with obliterating sclerosis in the arteries of the kidneys he found histologic changes resembling the glomerulonephritis which he supposes were the result of the sclerosis.

Diagnosis, therapy and prognosis.

The value of the acute mixed forms of pyelonephritic and diffuse glomerulonephritis lies therein that if one of the components is ignored it may have a detrimental influence on the fate of the patient. If a mixed form is considered to be a pure pyelonephritis the glomerulonephritis may develop in freedom and become chronic. If the pyelonephritis is ignored it may have a disturbing influence on the healing and further course of the glomerulonephritis. It seems, however, justifiable to *attach importance to the presence of hypertension, oedema, abundant proteins and casts in acute pyelonephritis.*

In chronic cases it may be impossible to state the differential diagnosis between a pure pyelonephritic contracted kidney and a mixed form when *the clinical picture of a diffuse glomerulonephritis appears simultaneously with an infected urine.* In practice it is not necessary to separate the two; it is important to state the differential diagnosis between pure glomerulonephritis on the one hand and the bilateral chronic pyelonephritis (pyelonephritic contracted kidney), and mixed forms on the other hand by examination of catheter urine in all cases of chronic glomerulonephritis.

Both components of the disease must be treated. The glomerulonephritis — whether acute or chronic — must be treated in the customary way. Against urinal infection every kind of urinal disinfectant may be used. In acute cases there is reason for waiting until the glomerulonephritis has improved somewhat and the diuresis and functions of the kidneys have improved. Sulphonamide should be the most effective in the case of bacterium coli and sulphathiazol in staphylococci. I have not personally noticed any complications when these remedies have been used despite heavy proteinuria and richness in sediment. Slight experience must exhort to caution in dosing. Almond-acid has been administered in some cases and no complications have arisen.

In chronic cases renal insufficiency does not seem to be an absolute counter indicator against urinal disinfectants. When placed before the probability that the patient may soon die of uremia the risks of a trial of treatment must be taken. We may find that cases of greatly reduced functions of the kidneys and increased non-protein nitrogen may improve to such a degree that the patient regains his ability to work.

Finally, there is reason to remember, both in the case of diagnosis and treatment, that there are rather numerous cases with infected urine where the infection occurs in the bladder only.

Summary.

Acute mixed forms of pyelonephritis and diffuse glomerulonephritis may arise as the results of angina tonsillaris (or other infections of streptococci). The clinical picture develops 1 to 4 weeks after the infection of the tonsils and shows symptoms of both these diseases: fever, urination troubles, pains in the back, pyuria and bacterium coli in the urine on the one hand, and hypertension, oedema, azothemia, oliguria, and nephritic sediment on the other hand.

Chronic mixed forms resemble greatly the chronic bilateral pyelonephritis (pyelonephritic contracted kidney) and may often not be separated clinically from each other. They probably arise partly from the acute forms, partly by a chronic glomerulonephritis adding itself to a pyelonephritis or vice versa.

The importance of the syndrome, diagnosis and treatment is being discussed.

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Studie über die diagnostische Bedeutung der Aniso-Makrocytose, speziell bei früher perniziöser Anämie.

Von

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(Bei der Redaktion am 28. April 1944 eingegangen).

Einleitung.

Die Diagnose der perniziösen Anämie ist in leichten Fällen oft schwierig, da die meisten Symptome bei einer Erythrocytenzahl von etwa 3 Millionen gewöhnlich wenig ausgeprägt sind.

Die Anamnese ist oftmals diffus, und die Angaben über u.a. Zungenbrennen und Parästhesien bedeuten nichts für Perniziosa Typisches oder Bindendes. Eine histaminrefraktäre Achylie muss praktisch als ein obligates Symptom angesehen werden, trotzdem das Vorkommen von freier Salzsäure im Magensaft nicht in jedem Fall perniziöse Anämie ausschliesst. Andrerseits ist eine unkomplizierte Achylie — besonders im höheren Alter —kein ungewöhnlicher Zustand. Das weisse Blutbild braucht auch nicht typisch zu sein, und Leukopenie mit relativer Lymphocythose und gesteigerter Kernsegmentierung kann fehlen. Eine erhöhte Plasmafärbung und Urobilinurie folgen in der Regel dem Grad der Anämie. Der Farbindex braucht nur kleine Abweichungen von der Norm aufzuweisen.

Um eine richtige Diagnose stellen zu können, kann man sich daher gezwungen sehen, entweder zu beobachten, ob die betreffende Anämie sich zu einer typisch perniziösen entwickelt, oder den Erfolg einer regelrechten Lebertherapie zu beobachten, durch die — wenn sie Erfolg bei hyperchromer Anämie mit histaminrefraktärer Achylie hat — die Diagnose sichergestellt wird. Dagegen wird die Reticulocytenkrise nach Lebertherapie bei perniziöser Anämie von ungefähr 3 Millionen unbedeutend und schwer zu beurteilen.

Eine Bestimmung des Durchmessers der roten Blutkörperchen wird ganz besonders nach den Untersuchungen von Price-Jones als diagnostisch wertvoll angesehen bei der perniziösen Anämie. In der Absicht, noch weiterhin zu untersuchen, in wie weit die Messung des Durchmessers zur Frühdiagnose verhelfen kann, wurden folgende Untersuchungen durchgeführt.

Methodik.

Frühere Untersuchungen:

Die Bestimmung des Durchmessers der roten Blutkörperchen kann nach verschiedenen Methoden geschehen, deren jede ihre Anhänger hat. Da ich mich in der folgenden Untersuchung ausser für den Mitteldurchmesser auch für die Verteilung nach Grösse interessiert habe, hat sich die Diffraktionsmethode oder Halometrie nicht geeignet, um so mehr als man — obwohl sie schnell und bequem ist — nicht ganz zuverlässige Werte damit erhält [Björk (11), Jörgensen und Warburg (62), Luckner und Tilger (69), Mogensen (77)].

Messung roter Blutkörperchen in ihrem Plasma oder Serum fallen meistens zufriedenstellend aus, da man dadurch eventuelle Veränderungen umgeht, die Ausstrich, Trocknen und Färbung bedingen. Aber das Anwenden dieser Methode war mir unmöglich, u. a. aus dem Grund, dass die von mir untersuchten Blutpräparate als Ausstriche arkiviert sind.

Bleibt also Messung vom Trockenpräparat. Die Veränderung, der die Blutkörperchen bei einer solchen Präparation ebenso wie bei der Färbung unterliegen, sind von den verschiedenen Untersuchern verschieden eingeschätzt worden. Bernstein (9), Günther (45), Heilmeyer (52), Ohno und Gisevius (84), Wiechmann und

Schürmeyer (105) finden keinen Unterschied des Mitteldurchmessers beim Messen am feuchten Präparat und am gefärbten Ausstrich. Dagegen geben Ponder und Millar (85) 12% Schrumpfung bei der Trockenmethode an, während Collatz (25) gefunden hat, dass Zellen im Plasma dagegen etwas kleiner sind. Gram (41) und Schulten (94) meinen, dass ausgesprochene Poikilocythose auf Trauma durch Ausstrich beruht. Bei Einbettung in Canadabalsam, oder wenn man Ölimmersion anwendet, wird nach Bernstein (9), Günther (45), Mogensen (77) und Ohno und Gisevius (84) der Mitteldurchmesser auf Grund der optischen Verhältnisse um bis zu 7 % verkleinert.

Ein Teil der Untersucher messen die roten Blutkörperchen direkt mit dem Okularmikrometer, was jedoch unbequem und anstrengend für die Augen ist und wo auch persönliche Faktoren freieren Spielraum gewinnen [Mogensen (77), Schalm (92)]. Price-Jones (86) u.a. haben sich daher der Projektionsmethodik bedient, durch die die Blutkörperchen vergrössert, abgebildet und gemessen werden. Mehrere Einwände haben sich jedoch hiergegen erhoben. Bock und Jombres (14) fanden z.B., dass Messung auf Mikrophotographien einen 0.45 μ grösseren Wert für den Mitteldurchmesser ergab als bei Anwendung von Okularmikrometer. Collatz (25) sowie Grosh und Stifel (44) fanden dagegen keinen Unterschied zwischen direkter und indirekter Messung.

Ebenso sehr wie die Ansichten über die Vor- und Nachteile der verschiedenen Messungsmethoden auseinandergehen, variieren die von den verschiedenen Forschern gefundenen Werte für den Mitteldurchmesser der normalen roten Blutkörperchen. Ich habe in der Literatur aus den Resultaten von 4 Forschern mit Halometrie als Mittelzahl des Mitteldurchmessers 7.6 μ gefunden. Die Messung von Zellen im feuchten Präparat mit Okularmikrometer hat Werte von 7.3 μ [Mc Cormic (74)] bis 8.2 μ [Borgbjaerg und Lottrup (17)] ergeben; als Mittel von 9 Untersuchungen 7.67 μ. Okularmikrometermessungen von Ausstrichen ergeben Werte von 7.2 μ [Heilmeyer (52)] bis 7.96 μ [Ohno und Gisevius (84)]; Die Mittelzahl von 13 Untersuchungen ergab 7.68 μ. Die Projektionsmethode, die Price-Jones (86) anwandte, ergab nach Messung von 500 Zellen von 100 verschiedenen, gesunden Individuen einen Mitteldurchmesser von 7.2 μ, während andere ähnliche Methoden höhere Werte ergeben haben [z.B. Schmoll (93) 8.15 μ]. Mittel-

zahlen von 9 Untersuchern 7.46 μ. Mit einer photografischen Methode bekamen Ponder und Millar (85) 8.8 μ.

Weitere Fehlerquellen, die zu berücksichtigen sind, sind die Wirkungen, die verschiedene physiologische und pathologische Zustände auf die Blutkörperchen haben können. Price-Jones (86), Hernberg (54), Keller (63), Schulten (94), Wichmann und Schürmeyer (105) fanden keinen Unterschied zwischen den Geschlechtern. Ohno und Gisevius (84) geben an, dass die Frau einen etwas grösseren Mitteldurchmesser habe als der Mann, während Schmoll (93) fand, dass der der Männer etwa 0.4 μ grösser ist. Hernberg (54) konstatiert, dass bei Erwachsenen der Mitteldurchmesser und die Anisocythose mit dem Alter etwas grösser werden. Die Blutkörperchen sind nach Bell, Thomas und Means (8) und Wiechmann und Schürmeyer (105) grösser bei Acidose, was nicht von Ponder und Millar (85) bekräftigt wird. Venenblut hat grössere Blutkörperchen als Arterienblut [Masel und Einhorn (73), Wichmann und Schürmeyer (105)]. Price-Jones (86) schreibt die bei Emfysem und grosser Anstrengung gefundene Durchmessererhöhung dem speziellen Einwirken von CO_2 zu. Bei forcierter Atmung und CO_2-Verlust schrumpfen die Blutkörperchen ein [Jørgensen und Warburg (62), Price-Jones (86)]. Nach Günther (45) ist dagegen die O_2-Spannung und Hämoglobinreduktion ohne nennenswerten Einfluss auf die Grösse der Blutkörperchen. Diese verschiedenen Faktoren können meistens als Fehlerquellen unbeachtet bleiben und die eventuellen Grössenveränderungen der Blutkörperchen sind meistens so unbedeutend, dass sie das Untersuchungsresultat nicht beeinflussen, wenn man nur bei Vergleichen keine Rücksicht auf allzu kleine Verschiedenheiten nimmt. Man sollte jedoch seine Blutproben unter den gleichen Bedingungen von Fall zu Fall nehmen.

Auf Grund der grossen Variation der von verschiedenen Forschern gefundene Normalwerte, ist ein jeder, der den Durchmesser der roten Blutkörperchen untersuchen will, gezwungen sich ein eigenes Normalmaterial zu verschaffen. Wenn die gleichen Bedingungen allen Bestimmungen zu Grunde liegen, werden die Werte völlig vergleichbar mit einander, was auch ich habe konstatieren können, indem ich in mehreren verschiedenen Ausstrichen von der gleichen Person die Blutkörperchen gemessen habe. Nach Günther (45) kann man ausserdem seine eigenen Resul-

tate mit denen anderer vergleichen, wenn man nur die gefundenen Werte ins Verhältnis zu den Normalwerten der respektiven Untersucher setzt.

Eigene Methodik.

Auf gewöhnliche Art genommene, luftgetrocknete, nach Pappenheim gefärbte Blutausstriche werden in einem Mikroskop mit einer lichtstarken Mikroskoplampe eingestellt. Ölimmersion. Ein auf Beinen stehender lichtdichter Kasten wird oben auf dem Mikroskop angebracht. Mitten im Boden des Kastens ist eine Öffnung, die dem Okular des Mikroskopes entspricht, und in der Mitte der Oberseite sind Deckel angebracht, die mit einer Mattglasscheibe oder einer gewöhnlichen Glasscheibe abwechselnd heruntergelassen werden können. Die Höhe des Kastens sei so gewählt, dass man eine Vergrösserung von genau 1 : 1000 erhält, was mit zwei verschiedenen Objektmikrometern kontrolliert wurde. Im Ausstrich wähle man für die Abbildung eine Stelle wo die Zellen dicht, doch frei voneinander liegen. Mittels der Mikrometerschraube des Mikroskops stelle man scharf auf die Mattglasscheibe ein, diese wird dann gegen die gewöhnliche Glasscheibe umgetauscht, auf die man ein Stück lichtempfindliches Papier legt und exponiert. Nach der Entwicklung misst man direkt auf diesen Negativen. Man erhält scharfe Bilder der Blutkörperchen, wenn man nur das Photopapier nicht zu gross wählt, da sonst die Konturen der Zellen in den Kanten unscharf werden. Ich habe 9 × 12 cm — Grösse angewandt. Zur Abbildung von 500 Zellen braucht man 6—8 derartige Papiere. Die Messung ist mit einem gradierten Stahlschiebmass (s. gen. Kolumbusmass) vorgenommen worden, dass man bis auf 0.2 mm = 0.2 μ nahe ablesen kann. Zerfetzte und stark deformierte Zellen sind ausgeschlossen worden. Da rote Blutkörperchen — wenigstens im Ausstrich — selten ganz rund sind, wurde der grösste und der kleinste Durchmesser ausgemessen, und der Durchmesser der Zelle entspricht dem arithmetischen Mittel dieser. Bei ausgesprochener Anisocythose wurden von jedem Patient 500 Zellen gemessen, bei normaler Verteilung 250.

Die oben angeführte Methodik ist bequem und nicht anstrengend und gibt ausserdem ein Foto des Blutbildes, das aufgehoben werden kann. Die eigentliche Messung ist natürlich zeitraubend. Man kann jedoch eine ganz gute Auffassung des roten Blutbildes gewinnen, wenn man nur 100 Zellen misst, was ungefähr 20 Minuten in Anspruch nimmt. Zeichnet man eine Verteilungskurve nach Price-Jones (86), so kann man Mitteldurchmesser und Anisocythose abschätzen und mit einer Normalkurve vergleichen. Um einen exakten Wert für diese Faktoren zu erhalten, charakteristisch für eine Price-Jones-Kurve, rechnet man das arithmetische

Mittel der gemessenen roten Blutkörperchdurchmesser aus. Als Mass der Anisocythose wurde die Dispersion (σ) angewandt, die nach folgender Formel ausgerechnet werden kann: $\sigma = \sqrt{\dfrac{\varepsilon \, p/x\text{-}M/^2}{n}}$.

Also die Wurzel aus der Summe der Frequenzen in jeder Klasse, multipliziert mit der Abweichung vom Medium im Quadrat, dividiert durch die Anzahl der Beobachtungen. Ausserdem habe ich noch — als ein drittes und wichtiges Charakteristikum eines roten Blutbildes — die Makrocythose in % ausgerechnet. Hiermit habe ich nach Jørgensen und Warburg (62) die Anzahl der Zellen gemeint, deren Durchmesser den normalen Mitteldurchmesser des Normalmateriales mit mindestens 1 μ überschreitet.

Selbst wenn im Sternalpunktat keine Megaloblasten nachweisbar sind, kann man im peripherischen Blut mindestens ebenso grosse rote Blutkörperchen finden, die dem Aussehen nach denen von eventuellem Megaloblastenursprung identisch sind. Ich habe es darum nicht für richtig gehalten, zwischen Makrocyten und Megalocyten zu unterscheiden, sondern alle roten Blutkörperchen über der oben angegebenen Grösse Makrocyten genannt.

Durch verschiedenartige Methoden eine eventuelle Inhomogenität der Distributionskurve des Durchmessers der roten Blutkörperchen, samt durch Bestimmung der Ovalität, Poikilocythose etc. der Blutkörperchen vielleicht ausserdem noch Anhaltspunkte für die Diagnose einer perniciösen Anämie zu erhalten, wird zu zeitraubend, um klinischen Wert zu haben.

Die Hämoglobinbestimmung geschah mit Sahlis oder Autenrieth-Königsbergs Hämometern; in beiden Fällen wurde der Wert in % angegeben. 100 % = einem Normalwert von 15.3 g Hämoglobin in 100 cm³ Blut [Enghoff (32)]. Der Icterusindex wurde nach Meulengrachts Methode bestimmt (obere Normalgrenze 6). Das Sternalpunktat ist von Docent Jan Waldenström auch untersucht worden. Mit typischen Megaloblasten — die die Diagnose der perniciösen Anämie sicherstellen — habe ich grosse Zellen mit luckerer Kernstruktur ohne Nucleolen, deren Protoplasma deutlich hämoglobinhaltig ist, gemeint.

Tabelle 1.

Normalmaterial.

Fall	Hb%	Rote Bltk.	M μ	σ	Makrocythose %
1. ♀	90	4.5	7.60	0.46	2
2. ♀	85	4.2	7.16	0.46	0.5
3. ♀	86	4.4	7.68	0.41	2
4. ♀	82	4.1	7.75	0.42	4
5. ♀	84	4.1	7.68	0.43	1.5
6. ♂	85	4.2	7.59	0.40	2
7. ♂	92	4.6	7.64	0.43	0.5
8. ♂	86	4.3	7.42	0.36	0
9. ♀	82	4.1	7.62	0.39	0.5
10. ♂	88	4.4	7.79	0.38	2
11. ♀	87	4.3	7.80	0.46	4.5
12. ♀	86	4.4	7.79	0.38	2.5
13. ♀	86	4.4	7.70	0.41	1.5
14. ♀	84	4.4	7.64	0.39	0.5
15. ♂	98	4.5	7.53	0.38	0
16. ♀	89	4.3	7.49	0.44	1
17. ♀	80	4.3	7.51	0.43	0
18. ♂	88	4.2	7.69	0.42	2
19. ♂	83	4.3	7.93	0.42	7
20. ♂	89	4.2	7.86	0.46	9.5

Normalwerte.

Als Normalmaterial wurden 20 angeblich gesunde Fabrikarbeiter im Alter von 20—40 Jahren mit normalen Blutwerten verwandt (Tabelle 1). Hiervon waren 12 Frauen und acht Männer. Ich habe von jeder Person 200 rote Blutkörperchen gemessen. Mitteldurchmesser (= M) variierte von 7.16 μ bis 7.93 μ mit einer Mittelzahl von 7.64 $\pm$ 0.165 μ. Verteilung (= σ) variierte von 0.36 μ bis 0.46 μ, als Mittelzahl 0.42 $\pm$ 0.028 μ. Ein Geschlechtsunterschied konnte nicht festgestellt werden. Wenn man die Beobachtungen, die ausserhalb $\pm$ 3 σ liegen, als pathologisch ansieht, nimmt man an, dass der Mitteldurchmesser für normales Blutzwischen 7.14 μ und 8.14 μ liegen soll. Ebenso soll die normale Verteilung nicht 0.50 μ übersteigen. Um aber gegen eine vergrösserte Anisocythose im Alter geschützt zu sein [Hernberg

(54)], habe ich eine pathologische Anisocythose erst als vorliegend betrachtet bei Werten ≥ 0.56 ($= 0.42 + 5\ \sigma$). Als Makrocyten habe ich rote Blutkörperchen $\geq 8.6\ \mu$ bezeichnet. Das Normalmaterial zeigt in keinem Fall mehr als 9.5 % Makrocythose, im Mittel 2.2 %. Pathologische Makrocythose liegt meiner Ansicht nach bei 15 % Makrocyten oder darüber.

Die Blutkörperchengrösse bei verschiedenen Krankheiten.

Kryptogenetische, perniciöse Anämie.

Schon zeitig hat man durch Messung Makrocythose bei perniciöser Anämie festgestellt, und in letzter Zeit haben zahlreiche Untersucher gezeigt, dass die typischsten Symptome im roten Blutbild der unbehandelten perniziösen Anämie der grössere Mitteldurchmesser und die grössere Anisocythose sind. Vergrösserter Mitteldurchmesser — jedenfalls bei unbehandelter perniciöser Anämie — ist so von z.B. Bock (13), Borgbjaerg und Lottrup (17), von Boros (18), Haden (46), Kirk (65) wie auch von Medearis und Minot (75) in zusammen 240 Fällen festgestellt worden. Die detailliertesten Untersuchungen sind von Price-Jones (86) an 68 Fällen ausgeführt worden. Er fand in allen diesen Fällen eine über das Normale hinaus gesteigerte Anisocythose und Makrocythose. Der Mitteldurchmesser war in allen Fällen, bis auf 5, erhöht. Diese letzteren gehörten zu einer Gruppe mit mehr ausgesprochener Anämie. Er gibt an, dass die Anisocythose direkt proportional dem Anämiegrad ist, und dass in diesen 5 Fällen der Mitteldurchmesser durch eine grosse Anzahl Mikrocyten gesenkt worden ist; aber der wirkliche Charakter der Anämie entschleierte sich durch die unnormale Anzahl grosser Zellen. Bell, Thomas und Means (8), die 25 Fälle untersucht haben, fanden eine deutliche Vergrösserung des Mitteldurchmessers, ausser in einem Fall, wo er innerhalb der Grenzen für die normale Abweichung lag. Sämtliche hatten verstärkte Anisocythose. Mogensen (77) hat 16 Fälle mit erhöhter Anisocythose beschrieben, von denen drei einen normalen Mitteldurchmesser hatten. Ebenso hat Mc Cormic (74) über eine ausgesprochene perniziöse Anämie berichtet, mit starker Anisocythose, wo jedoch der Mitteldurchmesser erst nach dem Verschwinden der

Mikrocythose während der Behandlung grösser wurde. Man meint, dass stärkere Mikrocythose, die den Mitteldurchmesser zum Sinken bringen kann, im allgemeinen erst bei Anämie unter zwei Millionen roter Blutkörperchen auftritt. In diesem Fall findet man eine pathologische Makrocythose die ein wichtiges Kriterium für den Typ der Anämie bildet.

In der Literatur wird angegeben, dass die Erhöhung des Mitteldurchmessers nicht proportional dem Grad der Anämie ist [Price-Jones (86), Goldhamer (39)], ebenso wie, dass die Makrocythose eines der frühzeitigsten Symptome darstellt [Haden (47), Schalm (92)]. Haden (47) hat 152 Fälle von perniciöser Anämie untersucht, die als Mittelzahl 1.81 Millionen rote Blutkörperchen per mm³ hatten, der höchste Blutwert war 3.68 Millionen. Ein typisch anisomakrocytäres Blutbild bei ungefähr 3 Millionen fand von Boros (17) in 4 Fällen. Medearis und Minot (75) konstatierten typische Züge für perniziöse Anämie bei einem Blutwert von 3—4 Millionen, aber fanden, dass das rote Blutbild bei einer höheren Blutkörperchenanzahl normal war. Reiners (87) hat 5 Fälle mit Anämie beschrieben, zwischen 3.32—4.05 Millionen, die alle hohen Mitteldurchmesser hatten. Haden (47) gibt an, dass bei höheren Blutwerten die Anisocythose entbehrt werden kann, trotzdem der Mitteldurchmesser weiterhin erhöht ist. Eine grössere Untersuchung des roten Blutbildes bei leichten Fällen von perniziöser Anämie habe ich in der Literatur nicht finden können.

Eigene Untersuchungen: Ich habe das Untersuchungsmaterial unter den Perniciosapatienten, die regelmässig in ihrem Krankheitsverlauf auf dem Akademischen Krankenhaus in Uppsala verfolgt wurden, ausgesucht. Ich hatte dabei Gelegenheit 18 zufällig ausgewählte Patienten zu untersuchen, deren Behandlung ausgesetzt wurde, um den Bedarf von Leberextrakt zu prüfen. Sie sind hierauf einmal per Monat kontrolliert worden, und nach einem Zeitraum von zwischen 6 Monaten und 3 ½ Jahren entstand wieder eine relativ moderate Anämie mit ca. 3 Millionen rote Blutkörperchen per mm³. In diesem Fall wurden die Blutuntersuchungen ausgeführt vor der erneuten Behandlung. Alle Patienten haben früher eine hochgradige, typische perniziöse Anämie gehabt, deren Diagnose durch ein typisches Sternalpunktat gesichert wurde, ebenso wie durch Lebertherapie, nach der auf typische Weise die Blutwerte bis zum völlig Normalen wiederher-

Tabelle 2.
Recidivierende perniciöse Anämien.

Fall		Alter Jahre	Hb %	Rote Bltk.	Index	M μ	σ	Makro-cythose %
1. E. Ö.	♀	69	76	3.0	1.3	8.46	0.64	44
7. K. C.	♀	39	75	2.6	1.5	9.34	0.78	84
8. A. W.	♂	71	75	3.0	1.3	8.95	0.68	66
9. I. K.	♀	68	70	2.7	1.3	8.98	0.72	73
10. E. B.	♀	79	79	3.1	1.3	9.10	0.68	76
11. B. A.	♂	64	84	3.1	1.4	8.64	0.60	57
14. A. B.	♀	46	87	3.0	1.5	8.26	0.64	31
15. O. N.	♂	56	91	2.8	1.6	8.50	0.63	46
18. T. W.	♀	57	74	3.1	1.2	8.45	0.74	41
19. S. M.	♀	69	75	3.3	1.1	8.49	0.67	45
21. O. O.	♂	79	79	3.4	1.2	8.79	0.60	64
23. A. P.	♀	63	75	2.9	1.3	9.09	0.56	85
24. A. G.	♀	68	79	3.4	1.2	8.57	0.56	42
32. M. P.	♀	73	79	2.6	1.5	9.64	0.69	94
33. J. W.	♂	66	71	3.1	1.2	8.60	0.64	48
34. H. B.	♂	58	67	2.5	1.3	8.73	0.80	61
42. C. F.	♀	74	70	3.1	1.1	8.19	0.61	27
52. H. J.	♀	66	68	3.3	1.0	8.08	0.68	22

gestellt wurden. Diese 18 Fälle sind also als sichere perniciöse Anämien zu betrachten, auf einem frühen Stadium, und es lag sicherlich keine der anderen Krankheiten vor, die sonst Makrocythose bedingen können. Die Sternalpunktion, die bei Gelegenheit der Blutuntersuchung gemacht wurde, gab in keinem Fall sichere Anhaltspunkte für perniciöse Anämie. Die Blutwerte und Resultate der Durchmesserbestimmungen sind in Tabelle 2 aufgeführt. Diese Fälle zeigten eine zunehmende Makrocythose ($>15\%$) und eine verstärkte Anisocythose ($\geqq 0.56$), die in den meisten Fällen sehr ausgesprochen waren. Der Mitteldurchmesser war in allen Fällen erhöht ($>8.14\ \mu$) mit Ausnahme von nr. 52, wo er dicht unter der Grenze für den oberen Normalwert lag. Ausserdem habe ich Gelegenheit gehabt, 6 nicht leberbehandelte, unkomplizierte Anämien mit histaminrefraktärer Achylie zu untersuchen, bei denen die Diagnose der perniziösen Anämie nicht mit Sicherheit durch Sternalpunktion und die übrigen Untersuchungsmetho-

Tabelle 3.

Neuentdeckte perniciöse Anämien (vorher unbehandelte).

Fall	Alter Jahre	Hb %	Rote Bltk.	Index	M μ	σ	Makro-cythose %
35. E. L. ♀	63	83	3.4	1.2	8.88	0.60	72
36. L. J. ♂	70	87	3.4	1.3	8.67	0.64	57
37. M. S. ♀	80	90	3.8	1.2	8.87	0.55	69
48. M. S. ♀	70	79	2.9	1.4	8.23	0.62	30
51. V. W. ♀	48	58	2.8	1.0	8.44	0.91	43
54. E. K. ♀	67	64	2.6	1.2	8.35	0.71	40

den gestellt werden konnte, wo man sie aber als gesichert ansehen kann auf Grund des Resultates der Leberbehandlung. In einigen Fällen wurde die Bestimmung des Serumeisens vor der Behandlung und am dritten oder vierten Tage nach der Behandlung vorgenommen. Kräftige Senkung desselben zeigten bei diesen Fällen, dass die Behandlung den gewünschten Erfolg gehabt hat.[1] Blut- und Durchmesserwerte gehen aus Tabelle 3 hervor. Sogar diese Früh-Anämien zeigen also ein für die perniziöse Anämie charakteristisches Blutbild.

Ein rotes Blutbild, das mehr oder weniger grosse Ähnlichkeit mit dem der essentiellen Perniciosa zeigt, kann jedoch bei Erwachsenen bei einer Anzahl verschiedener Krankheiten vorkommen, worauf man bei der Differentialdiagnose Rücksicht zu nehmen hat. In dem Folgenden habe ich einige Angaben aus der Literatur über das Blutbild bei derartigen Zuständen zusammengestellt, und in einigen Fällen eigene Untersuchungsresultate mitgeteilt.

Symptomatische perniziöse Anämie.

Die gleichen hämatologischen Befunde wie bei kryptogenetischer perniziöser Anämie findet man auch bei den Anämien, die man als symptomatisch perniziöse bezeichnen kann. Ätiologisch

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[1] Was die Bestimmung des Serumeisens während der Behandlung als Frühsymptom der perniciösen Anämie angeht, siehe J. Waldenström, Schweiz. med. Wochenschr., 1944, im Druck.

können diese Anämien, wenigstens in einem Teil der Fälle, als ein aus bekannten Gründen entstandener Mangel an antiperniziösem Princip leicht erklärt werden. Sie können ein für die perniziöse Anämie typisches Sternalpunktat aufweisen, und sie werden weiter dadurch charakterisiert, dass sie — ausser mit Lebertherapie — auch mit Entfernung des Grundleidens geheilt werden können. Es kann auch freie Salzsäure im Magensaft vorkommen. Anämien, die zu dieser Gruppe gehören, sind von vielen verschiedenen Forschern untersucht worden, und es konnten Price-Jones-Kurven aufgezeichnet werden, die typisch für perniziöse Anämie waren.

Symptomatische perniziöse Anämie ist von Groen und Snapper (43) in 2 Fällen nach langwierigem Diätfehler (Mangel an extrinsic factor) beschrieben worden. Diese beiden Fälle hatten freie Salzsäure im Magensaft und den Angaben nach typische Megaloblasten im Blut. Der eine Fall wurde allein mit vollwertiger Kost geheilt. Alsted (4) hat einen ähnlichen Fall beschrieben und hat ausserdem in der Literatur 32 seines Erachtens typische Fälle von perniciöser Anämie mit freier Salzsäure im Magensaft gesammelt, zu denen er zwei eigene derartige Fälle hinzufügt. Es ist ja möglich, dass ein Teil dieser Fälle der Gruppe: symptomatische perniziöse Anämie zugehört. Von den ca. 200 Fällen mit perniziöser Anämie aus dem Akademiska Sjukhuset in Uppsala war nur einer mit Salzsäure im Magensaft (»achrestische Anämie mit non-tropical sprue»).

Im Anschluss hieran wird auch die achrestische Anämie besprochen [Israels und Wilkinson (61)], die einen für die Perniciosa typischen Blut und Sternalpunktionsbefund aufweist, die freie Salzsäure im Magensaft zeigt und sich nicht bessert bei Lebertherapie. Es wird angenommen, dass der Grund hierzu das Unvermögen ist, aus der Leber das antiperniziöse Princip zu mobilisieren oder auszunutzen. Nielsen (80) beschreibt zwei ähnliche Fälle, die wie die tropische makrocytäre Anämie nicht von gereinigtem Leberextrakt gebessert wurden, aber wohl von diesem mit Zusatz von Vitamin B-Komplex.

Man ist sich einig darüber, dass hämatologisch typische perniziöse Anämie bei Sprue und idiopatischer Steatorrhoe entstehen kann [Hampson und Schackle (50), Jørgensen und Warburg (62), Malamos (71), Mogensen (77), Nielsen (80), Nordenson (82), Price-

Tabelle 4.

Verschiedene Anämien.

Fall	Alter Jahre	Hb %	Rote Bltk.	Index	M μ	σ	Makro-cythose %	Diagnos
60. A. A. ♂	65	51	1.5	1.7	8.44	0.76	42	A. pern. p. resect. ventr.
45. A. S. ♀	55	57	2.6	1.1	8.12	0.62	23	Cirrhosis Hepatis
84. S. L. ♀	70	84	3.4	1.2	9.08	0.58	84	» »
59. E. K. ♀	49	67	3.5	1.0	8.78	0.53	65	Hepatit. chron.
70. C. S. ♀	91	55	2.3	1.2	7.57	0.61	66	Leucaem. myeloblast.
73. I. G. ♀	63	38	2.1	0.9	7.90	0.61	14	» »
75. F. A. ♀	70	45	1.9	1.2	8.01	0.64	17	» »
72. B. Á. ♂	33	66	3.0	1.1	7.51	0.46	2	Cancer ventr.
79. G. L. ♂	59	53	2.0	1.1	7.53	0.58	7	» »
47. I. E. ♀	75	50	3.0	0.8	8.08	0.73	21	Purpura trombopenica
57. L. E. ♀	51	15	1.1	0.7	7.46	0.77	5	A. sideropenica
46. J. T. ♀	59	66	3.9	0.8	7.30	0.47	6	A. splenica

Jones (82), van Duyn (31), Vaughan (103)]. Ausserdem sind Fälle von perniziöser Anämie beschrieben worden, deren Entstehen man im Anschluss an verschiedene gastrointestinale Störungen erkannt hat, wie z. B. nach Gastrectomie, gastro-colischer Fistel, Dünndarmsstenosen, Ileitis, kronischer Diarrhoe [Borgbjaerg und Lottrup (17), van Duyn (31), Heath (51), Hurst (59), Jørgensen und Warburg (62), Nielsen (80), Schalm (92)]. In diesen beiden Gruppen soll die Ursache im Unvermögen einer Resorption der antiperniziösen Stoffe liegen.

Eine unklarere Ätiologie hat die perniciöse Anämie, die selten bei Schwangerschaft auftreten kann [Van Duyn (31), Naegeli (79), Nielsen (80) u. a.]. Und bei dieser trifft man auch auf Megaloblasten im Mark [Segerdahl (97)].

Zum Schluss will ich noch die perniziöse Anämie anführen, die in gewissen Fällen bei Personen mit Bandwurm vorkommt. Tötterman (102) hat 15 Fälle derartiger Anämie aufgeführt, die die für die Anämia perniciosa typische Price-Jones-Kurve aufwiesen. An Ätiologischem führt von Bonsdorff (16) an, dass man nach einer Wurmkur nur Remissionen bekommt (wie bei einer kräftigen Lebertherapie) wenn in der Nachrung reichlich extrinsic factor

vorhanden ist. Im Magensaft kommt der intrinsic factor vor, auf dessen eventueller Enzymwirkung der Wurm hemmenden Einfluss haben soll.

Eigene Untersuchung: Ich kann einen Fall von perniziöser Anämie mitteilen (Fall 60, Tabell 4) der sich nach Ventrikelresektion entwickelt hat.

Im Oktober 1935 wurde subtotale Gastrectomie vorgenommen auf Grund von Cancer cardiae, wobei nur ein Stumpf des Magens von 6 cm vom Pylorus zurückgelassen wurde. Die Blutwerte vor der Operation waren: hb 95 %, rote Blutkörperchen 4.3 Millionen. Im Mai 1940 waren hb 51 % und rote Blutkörperchen 1.52 Millionen. Das Sternalpunktat ergab keine Anhaltspunkte für perniziöse Anämie. Die Blutwerte stiegen jedoch gut an, als mit Campolon-Behandlung angefangen wurde, und der Patient fühlt sich noch 1943 ganz beschwerdenfrei. Die Durchmessermessungen vor der Behandlung zeigten — wie aus der Tabelle hervorgeht — Werte, die typisch für perniziöse Anämie sind.

Leberkrankheiten:

Der symptomatischen perniziösen Anämie scheint die makrocytäre Anämie nahe zu stehen, die man bei chronischen, ausgebreiteten Krankheiten in der Leber beobachtet hat. Solche Anämiefälle sind beschrieben oder erkannt von u.a. von Boros (18), van Duyn (31), Fellinger und Klima (35), Mogensen (77) so wie Schulten und Malamos (96). Bei einem grösseren Cirrosematerial fand Eppinger (33) Anämie in 51 %, in einem Teil der Fälle Anämie von makrocytärem Typ. Fellinger und Klima (35) haben bei der Untersuchung von 62 Lebercirrosen vom Typ Laennec in 65 % Anämie gefunden, wovon wiederum 65 % makrocytär waren. Rosenberg (89) konnte in fast 90 % von 48 Lebercirrose-Fällen Makrocythose konstatieren. Die unkomplizierte Anämie bei Lebercirrose zeichnet sich ausserdem dadurch aus, dass sie im Allgemeinen moderat ist [nach Rosenberg (89) als Mittelzahl für die roten Blutkörperchen 3.26 Millionen, nach Wintrobe (107) 3,47 Millionen], wie auch dass sie mit spontanen Remissionen zusammengehen kann, wodurch der rote Blutkörperchenmitteldurchmesser herabgesetzt wird [Wintrobe (107)]. Die Anisocythose wird im Allgemeinen als gering oder mässig angegeben, aber nach Wintrobe (107) und Wintrobe und Shumacker (108) ist die gleich der der perniziösen Anämie bei dem gleichen Blutwert. Mehrere Forscher geben

auch an, dass das rote Blutbild bei Lebercirrose sehr ähnlich oder rein unmöglich zu unterscheiden sei von dem einer moderaten perniziösen Anämie [Eppinger (33), Fellinger und Klima (35), Holler und Kudelka (58), Malamos (71), Wintrobe (107), u.a.]. Eine Achylie ist relativ gewöhnlich bei Lebercirrose [nach Wintrobe (107) in 40 %], muss sich aber nicht nachweisen lassen, damit eine makrocytäre Anämie entstehen kann. Glossitis wird von Fellinger und Klima (35) als ein nicht ungewöhnliches Symptom bei Lebercirrose angegeben, und van Duyn (31) hat einen Fall beschrieben, den er als eine Cirrose mit Glossitis und kombinierter Strangdegeneration deutet. Da das Vorkommen eines leichten Icterus auch in das Symptombild einer perniziösen Anämie eingeht, ist es verständlich, dass die Differentialdiagnose zwischen dieser Krankheit und Lebercirrose schwierig werden kann. Ausserdem geben mehrere Verfasser an, [Eppinger (33), Goldhamer (40), Isaacs (60), Wintrobe (107), Wintrobe und Shumacker (108), Vaughan (103)], dass sie bei der makrocytären Lebercirroseanämie Resultate von parenteraler Lebertherapie erzielt haben.

Auf der anderen Seite hat man nicht das typische Megaloblastenmark konstatieren können [Nordenson (82), Schulten (95)], selbst wo das Knochenmark in vielen Fällen als hyperplastisch angegeben wird, mit besonderer Steigerung der Proerythroblasten [Fellinger und Klima (35), Isaacs (60), Tischendorf (100)]. Viele Forscher haben ausserdem keinen oder nur unbedeutenden Erfolg der Lebertherapie beobachtet [Schulten (95)].

Anisomakrocytäre Anämien von wechselndem Grad sind auch bei anderen chronischen Leberkrankheiten beschrieben worden so wie bei Broncediabetes [Gamna (38)], chronische Herzinsuffiziens mit hochgradiger Leberstase [Frank und Hartmann (36), Luckner und Tilger (69), Malamos (71), Schulten und Malamos (96)] und bei ausgebreiteten Cancermetastasen [Dietrich (29)].

Bei sämtlichen oben genannten Leberkrankheiten ist ein ausgebreiteter Schaden erforderlich, für die Entstehung der Makrocythose. Die Makrocythose wird beträchtlicher im Takt mit dem Leberschaden und mit der Anämie, mit der auch die Anisocythose verknüpft ist. Die Makrocythose geht dagegen einem eventuellen Icterus nicht proportional.

Auf Grund ihrer Ähnlichkeit mit der perniziösen Anämie hat man versucht, auch die makrocytäre Lebercirroseanämie als durch

mangelnde Zufuhr des antipernizioösen Princips zum Knochen-
mark zu erklären. Eine Theorie ist, dass das gleiche schädliche
Agens, das die Lebercirrose ausgelöst hat, auch dem Magen
geschadet hat, sodass der intrinsic factor sich nicht bilden kann
[Eppinger (33), Hurst (59)]. Wintrobe und Shumacker (108) haben
jedoch bei einem Fall von perniciosa-ähnlicher Cirroseanämie
gezeigt, dass sich intrinsic factor fortlaufend bildet. Eine andere
Erklärung ist, dass die zum grossen Teil zerstörte Leber nicht län-
ger wie früher die antipernizioösen Stoffe aufspeichern und even-
tuel weiter verarbeiten kann [Goldhamer (40), Wintrobe (107)].
Goldhamer (40) hat auch in einem Fall gezeigt, dass die Leber
bei einem an Lebercirrose gestorbenen Patient mit perniciosa-ähn-
licher Anämie des antipernizioösen Prinzipes entbehrte.

Eigene Untersuchungen: Ich habe Gelegenheit gehabt, zwei
Fälle von Lebercirrose zu untersuchen (Fall 45 und 84, Tabelle 4),
die ein in allen Teilen der perniziösen Anämie gleiches Blutbild
aufwiesen. In Fall 45 lag eine histaminrefraktäre Achylie vor; in
Fall 84 ist der Magensaft nicht untersucht worden. Beide Patien-
ten wurden, ohne dass eine Wirkung hiervon sicher konstatiert
werden konnte, mit Leberinjektionen in solcher Dosierung behan-
delt, dass eine Remission hierdurch bei gewöhnlicher perniziöser
Anämie hätte eintreten müssen.

Akute Hepatitis: Etwas anders scheint das makrocytäre Blut-
bild sich zu verhalten, das man in den meisten Fällen von akutem,
diffusem Leberparenchymschaden beobachten kann (Hepatitis
acuta, akute gelbe Leberatrophie, Salvarsan-Icterus und bei ande-
ren Vergiftungen). Nach Hammarsten und Ståhle (49) tritt eine
deutliche Erhöhung des Mitteldurchmessers der roten Blutkörper-
chen bei einer akuten Hepatitis schon eine kürze Zeit nach den
ersten Krankheitssymptomen ein, selbst wenn der Icterus aus-
bleibt. Mehrere Forscher haben sogar konstatiert, dass ein Zusam-
menhang zwischen Makrocythose und der Stärke des Icterus nicht
vorliegt [Jørgensen und Warburg (62), Luckner und Tilger (69),
Rosenberg (89), Schalm (91)]. Die Price-Jones-Kurve bei diesen
akuten Leberkrankheiten wird nur durch eine Rechtsverschie-
bung ohne verstärkte Anisocythose charakterisiert [Hammarsten
und Ståhle (49), Schalm (92)]. Entwickelt sich später eine Leber-
cirrose, so verbreitet sich die Basis der Kurve und man erhält
das anisomakrocytäre Blutbild der Lebercirrose. Der Unterschied

in der Anisocythose kann man sich jedoch als darauf beruhend denken, dass im akuten Fall eine Anämie, mit der die Verbreitung verbunden ist, nicht vorliegt, während eine solche bei Lebercirrose gewöhnlich ist. Erholt sich der Patient nach einer akuten Hepatitis, geht der Blutkörperchendurchmesser rasch wieder auf das Normale zurück.

Die Ursache der Makrocythose bei akutem, diffusem Leberparenchymschaden ist umstritten. Mogensen (77) meint, dass sie auf osmotischen Veränderungen der roten Blutkörperchen, die schon in die Cirkulation eingetreten sind, beruht, da die Durchmesserstörungen in so kurzer Zeit auftreten können. Bethell und Rottschaefer (10) zeigen, dass — wenn cirkulierende Blutkörperchen anschwellen — ihre Hämoglobinkonzentration geringer werden muss, welches sie auch bei akuten Lebererkrankungen haben beobachten können. Bei Lebercirrose ist dagegen die Hämoglobinkonzentration normal, was auf eine Störung in der Erythropoese deutet. Rosenberg (89) gibt ungefähr der gleichen Meinung Ausdruck. Hammarsten (48) meint dagegen, dass gerade bei akuter Hepatitis eine Einwirkung von der einen oder andern Art auf das Knochenmark vorliegt, und stützt sich dabei auf einen Fall, wo die Price-Jones-Kurve einen Hiatus aufwies zwischen den neuauftretenden, normalgrossen Blutkörperchen und den zurückgebliebenen grossen während der Rekonvalescenz von einer akuten Hepatitis. Tischendorf (100) findet auch bei akuter Hepatitis eine stärkere Erythropoese im Knochenmark.

Die Bestimmung der roten Blutkörperchendurchmesser kann also bei akuten Leberkrankheiten diagnostische Bedeutung haben (Hepatitis sine ictero), ebenso wie prognostische Bedeutung (bleibende Erhöhung des Mitteldurchmessers, wenn die Leberkrankheit chronisch wird).

Eigene Untersuchung: Ich habe eine Kranke mit akuter Hepatitis untersucht, die in das chronische Stadium übergegangen ist (Fall 59, Tabelle 4).

Die Patientin wurde nach vorangehender Gesundheit am 21—12—1942 mit einer akuten typischen Hepatitis, mit Icterusindex 46 krank. Am 23—1—1943 war der Icterusindex bis 16 heruntergegangen, hb war 75 % und es waren 3,7 Millionen rote Blutkörperchen vorhanden. Die Patientin fühlte sich in der Folge nicht gesund, sie war müde und hatte einen Teil diffuse Schmerzgefühle im oberen rechten Teil des Leibes. Den 1—6—43

war die Leber 1 ½ Querfinger unter dem Rippenbogen palpabel, ebenso
konnte die Milz deutlich palpiert werden. Der Icterusindex war 7, also
an der oberen Normalgrenze. Der Mitteldurchmesser der roten Blut-
körperchen war in diesem Fall — wie aus Tabelle 3 hervorgeht — jedoch
deutlich erhöht. Die Anisocythose war dagegen gering. Die Blutunter-
suchung konnte bekräftigen, dass das Leberleiden nicht ausgeheilt war.

Hypothyreosis.

Die typische, unkomplizierte Anämie bei Myxödem wird von
Bomford (15) als eine moderate, mässig makrocytäre angegeben,
ohne stärkere Anisocythose und nicht beeinflussbar von Leber-
therapie, wohl aber von Thyreoideamedikation. Es wird angege-
ben, dass das gleichzeitige Vorkommen von echter perniciöser
Anämie und Hypothyreose gewöhnlicher sind als man erwarten
könnte, wenn nur zufälliges Zusammentreffen vorlag [v. Boros
(18), Bomford (15), v. Boros und Czoniczer (19), Holbøll (56),
Sharpe (98)]. In einem Teil der Fälle von reiner hypothyreoser
Anämie kann man jedoch das rote Blutbild unmöglich von dem
einer perniziösen Anämie unterscheiden. Derartige Fälle, die
alleine durch Thyreoidea-Behandlung gebessert wurden, sind von
Mackenzie (70), Meulengracht (71) und Holbøll (56) beschrieben
worden. Die makrozytäre hypothyreotische Anämie kommt sogar
ohne Achylie vor, trotzdem diese gewöhnlich bei Myxödem auftritt
[Bomford (15), Holbøll (55), Sharpe (98)]. Lerman und Means (67)
fanden, dass von 17 Hypothyreose-Patienten 9 histaminrefraktäre
Achylie hatten. 9 von diesen 17 Fällen hatten ausserdem Anämie,
die am meisten ausgesprochen in den Achylie-Fällen hervortrat.
Sie fanden doch auch bei Hyperthyreose einen grossen Prozentsatz
Achylie, doch haben unkomplizierte Basedow-Fälle eher Tendenz
zur Mikrocythose [Holler und Kudelka (57), Jörgensen und War-
burg (62)]. Bomford (15) hat gesehen, dass sich nach totaler Thyre-
oidectomie am Menschen makrocytäre Anämie entwickelt hat.
Als Ätiologie für die makrocytäre Anämie hat man die herab-
gesetzte Ventrikelsekretion als bedeutungsvoll angesehen [Bom-
ford (15), Lerman und Means (67)], ebenso wie die bei Hypo-
thyreose geforderte verminderte Knochenmarksaktivität [Bom-
ford (15), Sharpe (98)]. Mansfeld und Sós (72) haben gezeigt, dass
die Leber von Thyreoidectomierten Tieren fortlaufend anti-
perniziöse Stoffe enthält, weshalb sie die Theorie aufstellen, dass

Schilddrüsenhormon erforderlich ist, damit diese Stoffe zur Wirkung auf das Knochenmark kommen können.

Chronische Niereninsufficienz.

Was das Vorkommen von makrocytären Anämien bei chronischem Nierenleiden anbetrifft, welche in gewissen Fällen perniciosaähnlich werden können, sind die Ansichten sehr geteilt. Man ist in der Literatur einig, dass bei chronischen Nierenleiden sich eine mehr greifbare Anämie erst entwickelt, wenn Urämie-Symptome auftreten, und dass dann immer praktisch genommen echte Anämie vorliegt. Einige Verfasser meinen, dass die Anämie parallel mit der Resistickstoffsteigerung geht [Brown und Roth (20), Griva und Asinelli (42), Townsend, Massie und Lyons (101)], während andere dagegen einen Zusammenhang zwischen der Hochgradigkeit der Anämie und der Langwierigkeit der Urämie finden [Alexeieff (3), Faarup und Olsen (34)]. Urämieanämien werden von verschiedenen Verfassern beschrieben, [u.a. Becher (7), Brown und Roth (20), Csaki (26), Lachnit (66), Loeper und Perreau (68), Naegeli (79), Nerdenson (81)] als Hypo- oder Normochrome. Viele meinen mit Naegeli (79), dass, wenn man bei Urämie ein perniciöses Blutbild findet, es auf dem zufälligen Zusammentreffen der beiden Krankheiten beruhe. Goldhamer (39) hat einen solchen Fall beschrieben, der ausgezeichnet auf Leberbehandlung reagierte. Nylander (83) hat gefunden, dass, wenn eine Urämieanämie hypochrom ist, sich irgendwelche Komplikationen vorfinden. Griva und Asinelli (42), Isaacs (60), Malamos (71), Mogensen (77), Volterra (109) u.a. geben an, dass die Urämieanämie in einem Teil der Fälle hyperchrom, resp. makrocytär sein kann, dass aber im übrigen eine Ähnlichkeit mit perniziöser Anämie nicht vorkomme. Französische Verfasser haben in mehreren Fällen perniciosa-ähnliche Anämie bei chronischer Nephritis besprochen, da aber die Bezeichnung perniziöse Anämie offensichtlich schwerere Anämien für sie umfasst, als die essentielle Perniciosa, sind ihre Mitteilungen in einem Teil der Fälle nicht so aufschlussreich. Aubertin und Yacoel (6) haben jedoch den Fall eines 21-jährigen Urämiepatienten mit roten Blutkörperchen 1.1 Millionen per mm³, Farbindex 1.59 und einer ausgesprochener Anisocythose, sowie den eines 27-jährigen mit roten Blutkörperchen 1.7 Millionen, Farb-

index 1.6 und markierter Anisocythose beschrieben, also zwei rote Blutbilder, die von dem der echten perniziösen Anämie schwer zu unterscheiden sein müssen. In beiden Fällen war das Knochenmark zellarm. Diena (28) beschreibt einen chronischen Nephritpatient mit Anämie, Atrophie der Zungenschleimhaut, Achylie und Anisomakrocythose, wo eine Kombination mit perniciöser Anämie nicht vorzuliegen schien. Gamna (37) findet in beinahe allen Fällen von Urämie einen erhöhten Farbindex, und er behauptet, dass die Anämie perniciosa-ähnlich werden kann, aber dass man den Anisocythosetyp der Perniciosa nicht findet. Dasselbe fand auch Mogensen (77) in einem Fall. Nylander, der angibt, dass der Mittel durchmesser bei Urämieanämie meistens normal ist, beschreibt einen Fall mit erhöhtem Mitteldurchmesser und deutlicher Anisocythose. Die Leberbehandlung hatte in diesem Fall keinen Erfolg, der jedoch nur drei Wochen beobachtet wurde. Intravitale Knochenmarksuntersuchung zeigt bei Urämieanämie fast ein Bild von aplastischer Erythropoese nach Alexeieff (3), Faarup und Olsen (34), Lachnitt (66), Loeper und Perreau (68), Nordenson (81). Nordenson (82) hat jedoch später zugegeben, dass man sehr selten eine ausserordentlich starke Hyperplasie der Erythropoese finden kann, und dasselbe gibt auch Kienle (64) an. Townsend, Massie und Lyons (101) finden das Knochenmark normal oder hyperplastisch, und Isaacs (60) findet eine relative oder absolute Zunahme der primitiven Erythroblastzellen, von denen aus die weitere Reife zu roten Blutkörperchen normal, aber sparsam vor sich geht.

Die Ursache der Urämieanämie schiebt man ziemlich einheitlich dem Knochenmark zu, von dem man annimmt, dass es von verschiedenartigen toxischen Retentionsprodukten beeinflusst wird oder aber von den bei Hypertonie vorkommenden universellen Gefässschäden. Townsend, Massie und Lyons (101) weisen ausserdem darauf hin, dass die Funktionen des Magens eine Rolle spielen können. Sie fanden, dass von 19 Fällen mit Urämie fünf trotz Histamin-Stimulation keine freie Salzsäure im Magensaft aufwiesen, und sie geben an, dass immer bei einer CO_2-Kapazität unter 30 Volumen-% eine totale Achylie vorliegt. Es konnte jedoch kein pathologisch-anatomischer Schaden im Magen der an Urämie gestorbenen Patienten nachgewiesen werden.

Eigene Untersuchungen: Bei einer grossen Anzahl Urämiefällen habe ich vier angetroffen, bei denen das rote Blutbild von dem bei perniziöser Anämie nicht zu unterscheiden war.

Fall 44, C. J., ♀, geb. 1867:[1] Im März 1939 wurde zum ersten Mal Albuminurie konstatiert. Im Oktober 1939 bekam die Patientin Leibschmerzen und Erbrechen, weshalb sie am 14—10—39 im Akademiska Sjukhuset aufgenommen wurde. Sie wies ein unbedeutendes praetibiales Ödem auf und einen Blutdruck von 220/110. Die Nierenuntersuchungen zeigten leichte Albuminurie und bei der Wasserprobe eine ausgesprochene Isostenurie. Im Sediment fanden sich sparsame rote Blutkörperchen und einzelne körnige und hyaline Cylinder. Reststickstoff 66 mg %. Nach einer Probemahlzeit entschleierte sich eine histamin-refraktäre Achylie. Icterusindex 3. Takatas Probe negativ. Blutwerte: Hb 57 %, rote Blutkörperch 2.3 Millionen, Färbeindexen 1.2. M 8.55 μ, σ 0.61 μ. Makrocythose 47 %. Weisse Blutkörperchen 4800, davon 32 % Lymphocyten. Thrombocyten 419000. Reticulocyten 1.4 %. Das Sternalpunktat wies reichlich Normoblasten auf, gab aber keine Anhaltspunkte für perniciöse Anämie. Da die Patientin einer solchen trotzdem sehr verdächtig erschien, bekam sie 40 cm³ Campolon im Lauf von 4 Tagen; es konnte jedoch keine Wirkung auf Reticulocyten, Serumeisen oder Blutwert beobachtet werden. Nach der Ausschreibung verschwand die Patientin von der Kontrolle und kam erst am 2—6—43 auf Grund von Herzbeschwerden, Kopfschmerzen und Hautjucken wieder. In der Zwischenzeit hatte sie keine Leberbehandlung bekommen, mit Ausnahme einer Periode von drei Wochen im April 1943, wo sie von einem Privatpraktiker ein schwach wirkendes Per-os-Präparat ordiniert bekommen hatte.

Die Patientin zeigte auch jetzt nur ein unbedeutendes praetibiales Ödem. Blutdruck 230/110. Keine Nervensymptome. Albuminurie 0.5. °/₀₀ Im Sediment einige rote Blutkörperchen und körnige Cylinder. Reststickstoff 110 mg %. Takatas Probe negativ. Icterusindex 1. Blut: Hb 40 %, rote 1.7 Millionen, Färbeindex 1.2. M 8.61 μ, σ 0.64 μ. Makrocythose 54 %. Weisse Blutkörperchen 4300, wovon 24 % Lymphocyten waren. Reticulocyten 2.2 %. Thrombocyten 217000. Serumeisen 70 γ %. Resistenzprobe: beginnende Hämolyse bei 0.44 % NaCl, total bei 0.30 %. Das Sternalpunktat zeigte nichts für die perniciöse Anämie Typisches. Die Patientin bekam 7—6- bis 9—6-Heptomin i.m. 4 cm³ 3 Tage lang. 4 cm³. Heptomin wurden ausserdem den 29 – 6, 13—7. 19—8 und 23—9, i.m. gegeben. Ein Erfolg den Blutwerten gegenüber konnte nicht wahrgenommen werden, sondern sie waren den 30—9: hb 44 %, rote 1.8 Millionen. Dagegen konnte eine Senkung des Mitteldurchmessers und der Anisocythose konstatiert werden, den 13—7, da M 7.91 μ, σ 0.52 μ und die Makrocythose nur 12 % waren. Am 23—9 waren diese Werte wieder gestiegen: M = 8.11 μ, σ = 0.68 μ und Makrocythöse 24 %. Die Patientin starb am 8—10 nach gesteigerten Urämiesymptomen und einer Reststickstoffsteigerung bis zu 300 mg %. Die Sektion zeigte ausgesprochene Schrumpfnieren, aber im Übrigen nichts Bemerkenswertes.

Fall 56, M. D. ♀ geb. 1878: Schon 1896 wurde eine chronische Nephritis festgestellt, aber die Patientin war relativ beschwerdenfrei bis 1937,

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[1] Der Fall wird von J. Waldenström publiziert (Schweiz. med. Wochenschr., 1944).

als sie den 4—8. im Akademiska Sjukhuset aufgenommen wurde. Sie hatte da kein Ödem. Der Blutdruck war 195/140. Der Urin enthielt 2 %. Eiweiss und zeigte im Sediment mässige rote Blutkörperchen, aber keine Cylinder. Reststickstoff 67 mg %. Icterusindex 3. Histaminrefraktäre Achylie. Blutwerte: hb 68 %, rote Blutkörperchen 2.4 Millionen, Färbeindex 1.4. M 8.65 μ, σ 0.57 μ, Makrozythose 54 %. Reticulocythen 1.4 %. Thrombocythen 225,000. Weisse Blutkörperchen 5,200, davon 20 % Lymphocythen. Das Sternalpunktat zeigte nichts Bemerkenswertes. Die Patientin bekam Hepaforte per os ohne irgendwelchen Erfolg auf Reticulocythen oder die übrigen Blutwerte. Nach der Ausschreibung war die Patientin die ganze Zeit schwach und hatte Beschwerden mit Schwindel und Kopfschmerzen. Sie wurde aufs Neue im Krankenhaus aufgenommen, am 29. 10. 42. Da hatte sie deutliche Beinödeme. Blutdruck 220/115. Der Urin enthielt 8 %₀₀ Eiweiss, und im Sediment fand man reichlich rote Blutkörperchen. Der Reststickstoff war 145 mg %. Blut: hb 43 %, rote 1.8 Millionen, Index 1.2. M 8.82 μ, σ 0.71 μ, Makrocythose 68 %. Weisse Blutkörperchen 3500, mit 28 % Lymphocythen. Thrombocythen 175,000. Reticulocythen 0.8 %. Serumeisen 75 γ %. Das Sternalpunktat zeigte reichlich Normoblasten, im Übrigen aber nichts Bemerkenswertes. Die Patientin bekam Campoloninjektionen ohne Erfolg auf Reticulocythen oder die anderen Blutwerte. Am 12. 12. war hb 52 % und rote 2.4 Millionen. Sie starb unter Urämiesymptomen am 19. 7. 43. Bei der Sektion wurden ausgesprochene Schrumpfnieren konstatiert, aber im Übrigen nichts von Interesse.

Fall 71, K. A. ♂, geb. 1913: der Patient litt seit 1934 an einer chronischen Nephritis. Am 27. 8. 40 war hb 81 %, rote 3.1 Millionen, Färbeindex 1.3. Er wurde im Akademiska Sjukhuset am 31. 12. 42 aufgenommen, und hatte da deutliche Fussödeme. Urineiweiss 7 %₀₀. Reststickstoff war 212 mg %. Hb 33 %, rote 1.5 Millionen, Färbeindex 1.1. M 8.41 μ, σ 0.69 μ, Makrocythose 44 %. Das Sternalpunktat zeigte reichlich Normoblasten. Er starb gleich darauf unter zunehmenden Urämiesymptomen.

Fall 63, N. N. ♂ geb. 1877: die Nephritis des Patienten zeigte sich zuerst im Januar 1943. Hb war da 79 %, rote 4.82 Millionen, Reststickstoff 62 mg %. Den 5. 2. war der Reststickstoff 150 mg %. Am 19. 4. hb 47, rote 3.0 Millionen, Färbeindex 0.8. Thrombocythen 196,000. Weisse Blutkörperchen 6,900. Den 31. 5. war der Reststickstoff auf 40 mg % heruntergegangen, und es fanden sich nur Spuren von Eiweiss im Urin. Am 21. 6. hb 64 %, rote Blutkörperchen 3.7 Millionen, Index 0.9. M 8.23 μ, σ 0.57 μ, Makrocythose 28 %.

Diese 4 Fälle von Urämieanämie zeigten also alle ein rotes Blutbild wie das bei perniziöser Anämie. *Fall 44 und 56 sind auch* seinerzeit als solche gedeutet worden, und sie sind verschiedentlich mit Leberpräparat behandelt worden, ohne dass man einen Erfolg hätte beobachten können. Bemerkenswert ist die Abnahme des Mitteldurchmessers und der Anisocythose, die, ohne dass sich die

Blutwerte eigentlich verändert hätten, in Fall 44 nach einer mehr intensiven Lebertherapie konstatiert werden konnte. Als die Behandlung sparsamer wurde, ging wenigstens die Anisocythose zu ihren vorherigen Werten zurück. Eine Erklärung für diese Veränderung habe ich nicht, der Unterschied ist zu gross um von einem technischen Fehler bedingt werden zu können. Eine echte perniciöse Anämie dürfte nicht vorgelegen haben. Man könnte sich möglicherweise denken, dass bei gewissen Urämieanämien aus irgendeinem Grund das antiperniziöse Princip zerstört wird oder sich nicht bildet, wodurch die Anämien in diesen Fällen den Typus der perniziösen Anämie annehmen. Führt man dieses Princip in ausreichender Menge zu, so verschwinden die makrocytären Züge, die Anämie als solche wird jedoch nicht geheilt, da die Urämie als eigene Anämieursache zurückbleibt. In den drei Fällen, wo Sternalpunktion ausgeführt wurde, traf man im Knochenmark auf reichliche Normoblasten.

Dass bei Urämieanämie ein perniziöses rotes Blutbild vorkommen kann, ist also deutlich, und eine Bestimmung des Reststickstoffes im Blut müsste also auch aus diesem Grund zu den Rutineuntersuchungen bei perniciosaverdächtigen Blutkrankheiten gehören.

Lues.

Ein perniciöses Blutbild kann nach u.a. van Duyn (31) und Gamna (37) bei Lues vorkommen. Naegeli (79) hat einen derartigen Fall beschrieben, wo eine perniciosaähnliche Anämie durch Salvarsanbehandlung geheilt wurde, was der einzige Fall von luetischer perniziöser Anämie in der Literatur ist, der von Schulten (95) anerkannt wird.

Leukämie.

Nach Hinweisen aus der Literatur kann makrocytäre Anämie bei Leukämien verschiedener Typen vorkommen. So fanden Rosenthal und Harris (90) in einem grossen Material in einem Teil der Fälle hyperchrome, makrocytäre Anämie, manchmal perniciosaähnlich, und solche Blutbilder scheinen besonders bei aleukämischen Formen vorzukommen. Mogensen (77) fand erhöhten Mitteldurchmesser in zwei Fällen von leukopenischer, lymphatischer Leukämie, und in einem Fall war er so hoch wie bei perniciöser

Anämie, dabei lag im gleichen Fall auch erhöhte Anisocythose vor. Die Price-Jones-Kurve wurde jedoch nicht als perniciosaähnlich angesehen. Hampson und Schackle (50) haben bei einer aleukämischen Leukämie eine für die perniziöse Anämie völlig typische Price-Jones-Kurve gefunden. Schulten (95) meint, dass das rote Blutbild, besonders im anämischen Vorstadium einer Leukämie, schwer von dem der perniziösen Anämie zu unterscheiden sei. Vorkommen von Makrocythose bei Leukämie ist auch konstatiert worden von u.a. v. Boros (18), Brugsch (22), Csaki (26), Heilmeyer (52) und Murphy und Fitzhugh (78). Es ist also deutlich, dass das Blutbild bei aleukämischer Leukämie in einem Teil der Fälle dem der perniziösen Anämie ganz ähnlich werden kann, aber eine Sternalpunktion dürfte die Diagnose sicherstellen.

Eigene Untersuchungen: Ich habe einige Fälle von akuter aleukämischer Myeloblast-Leukämie (Fall 70, 73 und 75, Tabelle 4) untersucht, wo der Färbeindex nicht gesenkt war, und wo der Wert für die weissen Blutkörperchen nicht 5700 überstieg. Wie aus der Tabelle hervorgeht, war das rote Blutbild in diesen Fällen nicht ganz leicht von dem der perniciösen Anämie zu unterscheiden, da in Fall 73 die Makrocythose an der oberen Grenze des Normalen lag, und sie in Fall 75 gleich oberhalb dieser Grenze lag. Eine Sternalpunktion ergab in allen diesen Fällen die Diagnose unmittelbar.

Knochenmarkskrankheiten.

Naegeli (79) behauptet, dass man ein perniciosaähnliches Blutbild bei Knochenmarkstumoren, Knochenmarkskarzinom und Knochenmarkssepsis erhalten kann. Bock (13) hat mit dem Halometer Makrocythose bei Knochenmarksmetastasen gefunden, und Jörgensen und Warburg (62) sowie Schulten (95) geben an, dass dies in seltenen Fällen vorkommen kann.

Cancer.

Anämie bei Cancer in Verdauungskanal, besonders bei Cancer ventriculi, kann nach mehreren Forschern makrocytär sein. Ein Teil der Untersuchungen ist jedoch mit Halometrie ausgeführt, und Komplikationen wie akute Blutungen, Metastasen im Kno-

chenmark und der Leber ebenso wie die nicht so ungewöhnliche Kombination von Cancer ventriculi und perniziöser Anämie sind in gewissen Fällen nicht ausgeschlossen, weshalb die Angaben weniger zuverlässig werden.

Alder und Markoff (2) fanden mit Halometrie bei Cancer ventriculi oftmals Makrocythose, nicht beruhend auf der Lokalisation des Tumors oder auf einer eventuellen Achylie. Sie fanden dagegen keine Durchmessererhöhung bei Cancer in andern Teilen des Verdauungsapparates. Bock (12), der mit dem Halometer eine grosse Anzahl Fälle mit Cancer ventriculi untersucht hat, zeigte, dass in anämischen Fällen, wenn sich keine freie Salzsäure im Magensaft vorfand, sich oft Makrocythose vorfand, die unabhängig von der Lokalisation des Cancers und seiner Ausbreitung im Magensack war [Bock (13)]. Er konnte keine Makrocythose bei anderen Cancerformen aufweisen, wenn keine Leber- oder Knochenmarksmetastasen aufgetreten waren. Mit der gleichen Methodik stellte weiter auch Cheney (23) in acht von 43 Fällen mit Cancer ventriculi einen erhöhten Mitteldurchmesser fest. Keller (63) hat ausserdem einen erhöhten Mitteldurchmesser bei Cancer auch in anderen Teilen des Digestionsapparates gefunden. Aubertin (5) gibt an, dass Makrocythose und Anisocythose nicht nur bei Cancer ventriculi sondern auch bei Cancer coli vorkommen kann. Mogensen (77), der sorgfältige Messungen an einigen Fällen mit Magenkrebs gemacht hat, stellte in einem Fall erhöhten Mitteldurchmesser und Anisocythose fest, aber in diesem Fall war eine Kombination mit perniciöser Anämie höhst wahrscheinlich, trotzdem man die Price-Jones-Kurve nicht als vollauf typisch ansah. Ein anderer seiner Fälle zeigte einen hohen Mitteldurchmesser, aber normale Anisocythose. V. Boros (18) und Luckner und Tilger (69) finden nur leicht erhöhte Werte des Mitteldurchmessers in einem Teil ihrer Fälle von Ventrikelcancer. Borghjaerg und Lottrup (17) und Brugsch (22) haben keine Makrocythose bei dieser Krankheit nachweisen können.

Als Grund für Makrocythose bei Cancer ventriculi hat man sich einen Mangel in der Bildung von intrinsic factor oder eine mangelnde Resorbtion der antiperniziösen Faktoren gedacht. Megaloblastmark oder einen Erfolg von Lebertherapie hat man jedoch nicht konstatieren können.

Eigene Untersuchungen: Unter ungefähr 30 Fällen mit Cancer

ventriculi, die nicht mit perniziöser Anämie kompliziert waren, habe ich nur zwei antreffen können, deren Farbindex nicht gesenkt war. Diese beiden Fälle (Fall 72 und 79, Tabelle 4) zeigten, wie aus der Tabelle hervorgeht, keine Makrocythose.

Aplastische Anämie.

Bei dieser Krankheit hat Wintrobe (106) durch Blutkörperchenvolumenbestimmungen festgestellt, dass die Anämie makrocytär sein kann. Price-Jones (86) nennt zwei Fälle von aplastischer Anämie mit erhöhtem Mitteldurchmesser und gesteigerter Anisocythose, also das gleiche Bild wie bei perniziöser Anämie. Eine Sternalpunktion dürfte zur Diagnose helfen.

Thrombopenische Purpura.

Es werden zwei Fälle von Makrocythose bei einem derartigen Zustand von v. Boros (18) mitgeteilt, während Heilmeyer (52) ein normales rotes Blutbild gefunden hat.

Eigene Untersuchung:

Fall 47, Tabelle 4. Die Patientin kam zum ersten Mal im Januar 1943 mit einer thrombopenischen Purpura von unbekannter Ätiologie. Thrombocyten 15000. Weisse Blutkörperchen 6000 mit 30 % Lymphocyten. Keine Milzvergrösserung. Das Sternalpunktat zeigte reichlich Megakaryocyten, aber sonst nicht Bemerkenswertes. Es konnte kein Erfolg von Leberinjektionen nachgewiesen werden. Dieser Fall zeigte so einen Mitteldurchmesser an der oberen Grenze des Normalen, eine pathologische Makrocythose samt einer, trotz der mässigen Anämie, greifbare Anisocythose; mit anderen Worten ein Blutbild, das man bei einer moderaten perniziösen Anämie sollte finden können.

Splenomegale Anämien.

Heilmeyer (52) konnte in drei Fällen, die als Morbus Banti rubriziert waren, einen etwas erhöhten Mitteldurchmesser finden, während Vaughan und Goddard (104) einen normalen Durchmesser bei Anaemia splenica bekamen. Holler und Kudelka (58) stellten Mikrocythose bei gewissen Milzkrankheiten fest.

Eigene Untersuchung. Fall 46, Tabelle 4. Die Patientin ·hatte eine Anämie, Leukopenie und Thrompobenie sowie eine Milzvergrösserung. Die Durchmesserbestimmung ergab normale Werte. Nach Milzexstirpation trat eine Besserung der Blutwerte ein.

Hämolytische Anämien.

Unter dieser Bezeichnung werden eine Reihe verschiedener Anämieformen mit variierenden Symptomen zusammengefasst. Die Morphologie der roten Blutkörperchen ist in vielen Fällen nicht näher studiert, aber das Blutbild scheint in einem Teil Fälle dem der perniziösen Anämie ganz ähnlich werden zu können. Es ist allgemein bekannt, dass bei der gewöhnlichen familiären hämolytischen Icterusform fast immer eine Verringerung des Durchmessers der roten Blutkörperchen zu finden ist, trotzdem der Farbindex auf Grund von Sphärocythose nicht herabgesetzt ist. Die Ähnlichkeit mit einer perniziösen Anämie ist in diesen Fällen nur oberflächlich. Bei anderen essentiellen hämolytischen Anämien, die unter verschiedenen Namen beschrieben werden, z.B. Anämia Lederer, kann deutliche Makrocythose vorkommen [Dyke und Young (30), Kienle (64), Schulten (95)]. Das Material der Klinik in Uppsala ist von Dr. Glyn zu späterer Publizierung bearbeitet worden.

Übrige Zustände mit Makrocythose.

Dass nach einer akuten grösseren Blutung eine vergrösserte Anzahl Makrocyten in der Blutbahn auftreten kann, ist allgemein bekannt. Makrocythose im Blut ist ausserdem bei gewisse Vergiftungen festgestellt worden, wie mit Blei, Fenylhydrazin, Tetrachlorkohlenstoff, Arsen, Benzol und Toluol [Alder und Markoff (2), van Duyn (31), Gram (41), Haden (47), Heinle, Castle und Rose (53), Jörgensen und Warburg (62), Shumacker und Wintrobe (99).]

Diskussion.

Das rote Blutbild der perniziösen Anämie wird charakterisiert teils durch eine vergrösserte Anzahl grosser Blutkörperchen, welche verursachen, dass der Mitteldurchmesser fast immer deutlich erhöht wird, teils durch eine stärkere Anisocythose. Eine grosse Anzahl Mikrocyten kann jedoch bewirken, dass der Mitteldurchmesser nicht erhöht wird, aber eine pathologische Anzahl grosser Zellen zeigt, dass eine makrocytäre Anämie trotzdem vorliegt (siehe auch Fall 30 und 58). Weder Anisocythose oder Makrocythose . allein oder zusammen sind jedoch Beweise für eine perniciöse Anämie. Die Anisocythose, die im allgemeinen umso mehr zunimmt, je mehr die Anzahl der roten Blutkörperchen sinkt, kann bei jeder hochgradigen Anämie vollauf die gleichen hohen Werte erreichen wie bei einer perniciösen Anämie. Als Beispiel hierfür führe ich eine typische sideropenische Anämie an (Fall 57, Tabelle 4), bei der die Verbreitung ja bedeutend ist. Das einzige Typische bei einer Anisocythose bei perniziöser Anämie ist vielleicht, dass eine ausgesprochene Anisocythose frühzeitig vorzukommen pflegt, schon bei relativ mässigem Anämiegrad. Eine Anisocythose beruht ja auf einer erhöhten Anzahl kleiner Blutkörperchen oder auf einer vergrösserten Anzahl grosser oder auch auf beidem.

Ätiologisch ist zur Mikrocythose angeführt worden, dass das Knochenmark bei erhöhter Inanspruchnahme, bei überstürzter Ausschwemmung und besonders bei Insufficienz kleine Blutkörperchen liefert [Alder (1), Alder und Markoff (2), Bock und Jombres (14), Holler und Kudelka (58), Rohr (88)]. Weiterhin soll eine Störung in der Hämoglobinversorgung eine Anpassung an die verminderte Hämoglobinsynthese durch Produktion von kleineren Zellen verursachen [Alder (1)]. Besonders auffallend sollte dies bei Anämien auf Grund von Eisenmangel sein, die — wie allgemein bekannt ist — oft einen niedrigen Mitteldurchmesser der roten Blutkörperchen haben. Ich habe Gelegenheit gehabt, zwei Fälle mit Blutmangel zu untersuchen, welche als typische Anämien mit Eisenmangel begannen, bei denen sich aber allmählich eine sichere perniziöse Anämie entwickelte.

Fall 30, A. G. ♀, geb. 1874. In mehreren Jahren bleich und müde. Wurde im Akademiska Sjukhuset am 20—11—1936 aufgenommen. Die Probemahlzeit zeigte eine histaminrefraktäre Achylie. Icterusindex 4. Blut: hb 45 %, rote Blutkörperchen 2.7 Millionen, Index 0.8. M 7.89 μ, σ 0.95 μ, Makrocythose 24 %. Sternalpunktion: normales Knochenmark. Die Patientin wurde mit Eisenpräparat behandelt, wodurch die Blutwerte stiegen, sodass am 11—2—37 hb 63 % war und rote 3.5 Millionen. Trotz fortgesetzter Eisenmedikation zu Hause wurde die Patientin doch wieder schlimmer und wurde wiederum am 18—4—37 aufgenommen. Sie zeigte jetzt Nervensymptome in Form von herabgesetzter grober Kraft im rechten Bein und positiven Babinskireflex am linken Fuss. Icterusindex 25. Blut: 18 %, rote 0.7 Millionen, Index 1.3. Das Sternalpunktat zeigte zahlreiche typische Megaloblasten. Mit alleiniger Campolonbehandlung erzielte man einen ausgezeichneten Erfolg, so dass am 5—7—37 hb 86 % war und rote 5.2 Millionen.

Fall 58, J. B., ♀, geb. 1864. (Der Fall ist von J. Waldenström in Nordisk Medicin 1941, Seite 2345 publiziert worden.) Die Patientin wurde 1931 im Akademiska Sjukhuset für Anämie gepflegt. Damals hb 50 %, rote 4.7 Millionen, Index 0.5. Besserte sich gut mit Eisen. Wieder aufgenommen am 14—6—1938 und zeigte da ausgesprochene Koilonychie. Keine freie Salzsäure im Magensaft, trotz Histaminstimulation. Icterusindex 4. Hb 30 %, rote 1.7 Millionen, Index 0.9. M 8.23 μ, σ 1.06, Makrocythose 40 %. Thrombocyten 96000. Reticulocyten 3.8 %. Das Sternalpunktat zeigte normales Knochenmark. Sie wurde nur mit Eisen behandelt, und am 26—7—38 war hb 80 % und rote 4.5 Millionen. Auf Grund von Anämie wurde die Patientin aufs Neue am 10—1—41 aufgenommen. Icterusindex war da 11, hb 26 %, rote 0.9 Millionen, Index 1.4. Sternalpunktion: typische Megaloblasten. Mit Campolonbehandlung bekam man eine deutliche Reticulocytenkrise, und die Blutwerte waren am 28—1—41 hb 66 %, rote 2.8 Millionen.

Aus diesen Fällen geht hervor, dass trotz Eisenmangels mit seiner Tendenz zur Mikrocythose die Makrocythose der perniciösen Anämie schon in einem frühen Stadium deutlich war, wenn auch die grossen Zellen auf Grund ihrer relativen Minderzahl keine stärkere Erhöhung des Mitteldurchmessers haben verursachen können. Es hätte also in beiden Fällen schon bei der ersten Untersuchung (1936 resp. 1938) der Verdacht auf eine perniciöse Anämie entstehen können, wenn man damals eine Durchmessermessung vorgenommen hätte, und nicht wie jetzt erst hinterher.

Dass Makrocythose ausser bei perniciöser Anämie auch bei einer Reihe verschiedener Krankheiten vorkommen kann, ist im Vorhergehenden beleuchtet worden. Eine Erklärung für die Bildung von abnorm grossen Zellen hat man im allgemeinen mit

mehr oder weniger gutem Grund gesucht in einem aus verschiedenar-
tigen Gründen entstandenem Mangel an antiperniziösem Princip,
welches ja erforderlich ist, damit die blutkörperchenbildenden
Zellen im Knochenmark auf normale Weise reifen können. Ist
der Mangel hochgradig, so bekommt man eine totale Blockade der
Erythropoese, die umschlägt und megaloblastisch wird, so wie
bei essentieller und symptomatischer perniciöser Anämie. Dass
ausgesprochene Makrocythose durch einen solchen Mangel auch
ohne megaloblastische Blutbildung auftreten kann, ist ja bekannt
von den Fällen von perniziöser Anämie, bei denen Knochenmarks-
veränderung nicht konstatiert werden kann, was auch meine frü-
hen Fälle zeigen. Es dürften sich auch andere Erklärungen für
Makrocythose finden lassen, hierfür spricht ja u.a. das Faktum,
dass in vielen Fällen mit makrocytären Anämien kein Erfolg mit
Lebertherapie aufweisbar ist.

Eine ausgesprochene perniziöse Anämie ist leicht zu diagnosti-
zieren, es können aber, worauf in der Einleitung hingewiesen wurde,
Schwierigkeiten bei weiniger ausgeprägten Anämiegraden ent-
stehen. Aus Angaben in der Literatur wie aus eigenen, hier mit-
geteilten Untersuchungen geht hervor, dass deutliche Aniso-
makrocythose schon bei relativ geringer Anämie vorkommt, weshalb
eine Messung des Durchmessers der roten Blutkörperchen von
grossem diagnostischem Wert in diesen Fällen sein kann. Gewiss
kann ein gleiches oder ähnliches Blutbild bei anderen Krankhei-
ten vorkommen, worauf man Rücksicht nehmen muss; besonders
will ich Lebercirrose, Hypothyreose, Urämie und aleukämische
Leukämie hervorheben. Kommt aber eine Makrocythose und eine
grössere Anisocytose bei einer histaminrefraktären Achylie vor, so
wird eine perniciöse Anämie sehr wahrscheinlich. Noch wertvol-
ler wird die Messung des Durchmessers dadurch, dass man zu
behaupten wagt, dass — wenn keine pathologische Makrocythose
bei Anämie mit 3 Millionen roten Blutkörperchen oder darunter
vorkommt — eine perniziöse Anämie ausgeschlossen werden kann.

Zusammenfassung.

1. Eine Projektionsmethodik zur Messung des Durchmessers
roter Blutkörperchen wird angegeben. Der Normalwert des Mittel-
durchmessers war 7.64 μ.

2. Es wird auf die Schwierigkeiten für die Frühdiagnose der perniziösen Anämie hingewiesen. Der Verfasser hat 18 längere Zeit unbehandelte, sichere perniziöse Anämien mit einem Blutwert von ungefähr 3 Millionen rote Blutkörperchen per mm³, und 6 neuentdeckte perniziöse Anämien mit dem gleichen Anämiegrad untersucht. Alle diese zeigten typische Anisomakrocythose.

3. In keinem von diesen 24 Fällen konnte die Diagnose perniziöse Anämie durch den Befund aus der Sternalpunktion gestellt werden.

4. Durch Literaturreferat wie durch eigene Untersuchungen wird gezeigt, dass ein dem der perniziösen Anämie gleiches oder ähnliches rotes Blutbild bei einer Anzahl Krankheiten vorkommen kann.

5. Der Verfasser will besonders betonen, dass ein dem der Perniziosa gleiches Blutbild bei Urämie in 4 Fällen gefunden wurde.

6. Eine Anisomakrocythose bei histaminrefraktärer Achylie macht die Diagnose perniziösen Anämie höchst wahrscheinlich.

7. Kommt bei einer Anämie mit 3 Millionen rote Blutkörperchen oder darunter keine Makrocythose vor, kann perniziöse Anämie ausgeschlossen werden.

Der Verfasser dankt Docent Jan Waldenström für den Vorschlag zu dieser Arbeit sowie für Anweisung von Patienten zur Untersuchung mit früher perniziöser Anämie, die für Serumeisenuntersuchungen zusammengestellt waren. Der Verfasser dankt auch für Ratschläge bei der Durchführung der Arbeit.

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The Intrinsic Factor Activity of Highly Purified Preparations of Aminopolypeptidase.

By

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I. Chemical and Physiological Part, by GUNNAR ÅGREN.

In 1929 Castle advanced the theory that an external, »extrinsic» factor (present in food) and an internal »intrinsic» factor (present in gastric juice) on interaction gave rise to a substance which was active against pernicious anemia. In 1934 Meulengracht localized the intrinsic factor to the pyloric-duodenal region of the alimentary canal. Reimann (1931), Walden and Clowes (1932) and Wilkinson (1933) made investigations on the properties of the intrinsic factor. Based on the results of these Wilkinson considered that the factor was of enzymatic nature. Later on it was demonstrated that the enzyme was not identical with pepsin, rennin, kathepsin or lipase.

In a series of papers the present author has advanced the theory that the intrinsic factor of Castle might be identical with the enzyme aminopolypeptidase present in pyloric and duodenal mucosa (Ågren, 1942 a and b, 1943). In brief the experiments reported in these papers demonstrated that intravenous injections of crystalline secretin provoked on cats a secretion from the mucous membrane of the distal part of the pyloric and the proximal part of the duodenal region, the part of the alimentary canal from which the intrinsic factor is considered to be secreted. (Meulengracht 1934, Wallgren 1943, Strunge 1944). The secretion contained a rather high concentration of aminopolypeptidase. In accordance with the

results obtained by Castle it was demonstrated that an enzymatic reaction (proteolysis) took place after incubating the secretion with a muscle extract. When purifying the aminopolypeptidase from the hogs pyloric mucosa it was found that the purified enzyme solution apparently contained most of the intrinsic factor activity present in the mucous membrane. The intrinsic factor activity was estimated by allowing the purified enzyme solution to react with liver according to the method outlined by Reimann 1931 and Sjögren (1940). At this stage of the investigation (1941) the aminopolypeptidase had been purified about ten times. The possibility could therefore not be excluded that the parallelism was but a mere coincidence. Since then the enzyme has been further purified about ten times, in all, about a hundred times. In the present paper the method of purifying the enzyme is briefly described and the intrinsic factor activity of this highly purified material is reported.

Experimental.

I. Chemical Methods. Protein nitrogen was determined by the micro-Kjeldahl procedure. Traces of ammonium sulphate contaminating the dialysed solutions necessitated a preliminary precipitation of the protein with trichloracetic acid. Usually 1 ml of solution containing 0.2 mg of nitrogen was precipitated with 2 ml of 10 % trichloracetic acid. After heating for two minutes at 100° C the mixture was cooled in tap water, the precipitate centrifuged and washed twice with 2 % trichloracteic acid and hydrolyzed with concentrated sulphuric acid.

Total Carbohydrates were estimated by the method of Tillman-Philippi in the modification of Sörensen and Haugaard (1933).

Aminopolypeptidase activity was determined by the micro method of Linderström-Lang and Holter (1931). A 0.2 mol solution of alanyl-glycyl-glycin was used as substrate. The digestions were carried out at 40° C for 30 minutes using 7 mm³ of substrate and 7 mm³ of enzyme solution. In the titrations n/20 HCl was used.

II. Method of Preparation. As previously described, the hogs' dried pyloric mucosa (Stotal made by the Astra Corporation, Södertälje, Sweden) contains about 50 % of the aminopolypeptidase activity of the fresh pyloric mucosa (Ågren, 1942 b). From this substance the enzyma was usually prepared. The method which was finally adopted is briefly summarized in the following.

1) 100 g of Stotal powder were extracted with 2000 ml of a 0.35 saturated solution of ammonium sulphate in m/10 sodium bicarbonate by shaking for 2 hours. The unsolved was separated by centrifugation and the solution brought to 0.9 saturation by adding solid ammonium sulphate. The suspension was allowed to settle for 1 hour and filtered after addition of 7 g of coarse (Hyflow) Cel on 30 cm Buchner funnels covered with filter paper and with a layer of coarse Cel. The filtrate was discarded.

2) 100 g of the above filter cake were extracted with 500 ml of 0.1 M pH 7.4 phosphate solution and the filter Cel separated by centrifugation. The centrifugate was dialysed during constant stirring in thin cellophane tubes against 0.01 M pH 7.4 phosphate solution. After 4 hours of dialysis the solutions were almost freed of ammonium sulphate. This solution was used in the first investigation as to the intrinsic factor activity of the purified aminopolypeptidase solution. (Ågren, 1942 b).

3) The dialyzed solution from 2) was diluted with destilled water until the concentration of protein nitrogen was about 0.8 mg per ml of solution and heated to 50° C for 3 minutes. The solution was then precipitated with optimal amounts of a 0.5 N solution of lead acetate, usually about 60 ml per 1000 ml of enzyme solution. The lead precipitate was separeted by centrifugation and the filtrate neutralized to pH 7.4 with sodium hydroxide. When proceeding in this manner, there usually occurred an opalescence which was removed by separation. The clear solution was concentrated in vacuum at 15° C to a tenth of the original volume.

4) The concentrated solution from 3) was brought to 0.8 saturation of ammonium sulphate in m/10 sodium bicarbonate by adding solid ammonium sulphate and sodium bicarbonate. About 3 g of coarse Cel were added and the suspension filtered on a Buchner funnel covered with a layer of coarse Cel. The weight of a moist cake of precipitated enzyme was about 15 g. The filtrate was discarded.

5) Four cakes from 4) were extracted with 100 ml of a m/10 pH 7.4 phosphate solution. The Cel was separated by centrifugation and the solution dialysed for 2 hours against a M/100 pH 7.4 phosphate solution. The dialysed solution was brought to 0.6 saturation of ammonium sulphate and M/10 sodium bicarbonate by adding the solid salts. About 3 g of coarse Cel were

Table 1.

The numbers refer to the figures of the different steps of the method of preparation given in the text.	Time of handling Hours	Protein nitrogen mg/ml	Activity in ml n/20 HCl		Per cent of activity original	Carbohydrate (as glucose)	
			1/mm³	1/mg P. N.		mg/ml	activity in ml n/20 HCl per mg of glucose
1	6	120	0.060	0.50	100	0.04	1.20
2	6	0.8	0.006	7.0	92	0.06	9.50
3	4	1.0	0.036	36.0	60	1.4	26.0
4	4	3.9	0.125	33.0	55	4.8	26.0
5	4	4.5	0.180	40.0	40	4.0	45.0
6	3	6.0	0.40	66.0	25	4.0	100.0

added and the suspension filtered on a Buchner funnel covered with a layer of coarse Cel. The filtrate was discarded.

6) The filter cake from 5) was extracted with 70 ml of M/10 pH phosphate solution. The filter Cel was separated by centrifugation and the solution dialysed for 2 hours during constant stirring against M/100 pH 7.4 phosphate soliton. The dialysed solution was brought to 0.5 saturation of ammonium sulphate in M/10 sodium bicarbonate by adding the solid salts. The precipitate was centrifuged in a Beam ultracentrifuge.

Quantitative data from the different stages of the preparation are given in Table 1.

III. Method of Demonstrating the Intrinsic Factor Activity of the Aminopolypeptidase Solution. The intrinsic factor activity was estimated by allowing a sample of the one a hundred times purified enzyme solution to react with raw liver according to the principles outlined by Sjögren (1940). He assumed that liver, like meat, would contain extrinsic factor. This assumption proved correct because the properties of the liver were found to be extremely satisfying in this respect, considerably more satisfying than any other material that had been tested. Pyloric mucosa was used as source of intrinsic factor. The two factors were allowed to react under certain conditions and in optimal relations. In this reaction the effect of the liver preparation — Hepaforte, Astra — became 10 times stronger so that the »liver material» which was considered adequate for an orally administered maintenance dose in the treatment of pernicious anemia in man was obtained from only 25 g of the calf's activated liver instead of from 250 g of non-activated liver.

The estimation of the intrinsic factor activity of the purified aminopolypeptidase solution was based on the following experimental results: The concentration of aminopolypeptidase in the fresh pyloric mucosa was determined. Thereupon it was easy to calculate, the amount of enzyme activity present in the sample of pyloric mucosa used by Sjögren as intrinsic factor material. The next step was the determination of the aminopolypeptidase activity of the vacuum-dried pyloric mucosa. This was the material from which the enzyme of the present investigation was prepared. It was found that half of the original aminopolypeptidase activity was left after the desiccating process. As 1 g of the dried material was prepared from 6 g of fresh material it was easy to calculate how much of the purified enzyme would be used in the activating experiment.[1] In the course of this, the aminopolypeptidase from 10 kg of vacuum-dried pyloric mucosa was purified according to the method given above. As the method yielded about 25 %, the amount of the aminopolypeptidase activity in the solution of the one hundred times purified enzyme was the same as in 2.5 kg of vacuum-dried or 7.5 kg of fresh pyloric mucosa. The solution was divided into halfs (dry weight of each = 10.5 g) One half of the solution was substituted for the intrinsic factor activity of 3.7 kg of fresh pyloric mucosa in the activation of raw liver. This preparation was called number 2. In preparation number 1 the other half of the enzyme solution was substituted for the intrinsic factor activity of 7.5 kg of fresh pyloric mucosa. It was assumed that, if the intrinsic, factor activity had really been purified parallel with the aminopolyeptidase activity, then it should be even possible to trace the activating effect of half of the optimal dose of intrinsic factor on liver. The activating experiments were carried out by Sjögren at the Astra Corporation. The daily therapeutical dose of the preparations 1 and 2 contained material from about 30 g of fresh, activated raw liver. In the clinical part of this work it is shown that both preparations are active when tested on patients suffering from pernicious anemia.

Results and Discussion.

One of the two main results in the present paper is the demonstration of a method by which the enzyme aminopolypeptidase

may be purified a hundred times. The details of the method together with a report of some of the chemical and physiological properties of the enzyme will be published elsewhere. In this paper only a brief summary is given. In this connection it must be emphasized that usually such a high degree of purification has not been found necessary in the isolation in crystalline form of other proteolytic enzymes of the alimentary canal.

The other main result of the present investigation is the demonstration of the close correlation existing between the intrinsic factor and the enzyme aminopolypeptidase of the pyloric mucosa. During the whole method of purification involving a rather long and complicated series of chemical procedures, the intrinsic factor activity of the original material seems to have paralled the activity of aminopolypeptidas. This strongly favors the authors hypothesis of the existence of a relationship between these two factors of the pyloric mucosa even in face of the fact that it will not be possible to furnish definitiv proof before aminopolypeptidase can be isolated in pure form.

Until recently the attempt to investigate what kind of reaction takes place between extrinsic and intrinsic factors as well as its determination has not been especially tempting. One of the reasons is that both the reaction product of intrinsic factor — the active factor of the liver — and especially the substrate — the extrinsic factor — have not been isolated in sufficiently pure state. The enzymatical specifity of intrinsic factor has also been unknown. At present, however, recent investigations in this field have brought forth results which seem to promise that the nature of the reaction between extrinsic and intrinsic factors may be unveiled.

Bonsdorff (1943) demonstrated that in patients with pernicious tapeworm anemia, who were given a diet consisting of carbohydrates, fat and vegetables and which therefore presumably waś poor in Castle's extrinsic factor, blood remission failed to set in after the expulsion of the worm. If, however, substances rich in protein and probably containing the extrinsic factor were added to the diet, the blood values improved quickly. Thus remission set in following the administration of meat, milk, Hammarsten's casein, commercial pepton, brewer's yeast and of a concentrated yeast extract as well as — although to a lesser degree — of soy bean protein. On the other hand the antipernicious principle of the liver

is supposed to be a dialysable polypeptide with a molecular weight ranging between 2000 and 5000 (Dakin and West, 1936; Karrer, 1941, 1943). Thus both, the substrate and the reaction product of the intrinsic factor, seem to be related to protein-like substances and therefore the assumption is permissible that the intrinsic factor might be a proteinase possibly the aminopolypeptidase, which according to the authors investigations is secreted from the pyloric-duodenal region of cats during the influence of secretin. The results of the present investigation support the assumption of a close relationship between the intrinsic factor and aminopolypeptidase. In such case the presumable function of the intrinsic factor would be to set free certain amino acids or combinations of amino acids which are a necessary part of the liver factor. If this view is correct then the aminopolypeptidase is not likely to attack the antipernicious liver factor in spite of its character of a peptide. This assumption was verified (Ågren, 1943). If aminopolypeptidase was identical with intrinsic factor one cannot but assume that the interaction between extrinsic and intrinsic factors must take place at a pH = 5. The recent investigations of Castle and coworkers (1939) seem to bear out that this is the case.

Summary.

The enzyme aminopolypeptidase from the hog's pyloric mucosa was purified a hundred times. As illustrated in the clinical part of this paper the intrinsic factor activity of the pyloric mucosa seems to have closely followed the aminopolypeptidase activity through all the stages of the — preparation method. This fact strongly supports the author's view that the intrinsic factor may be identical with the aminopolypeptidase in the pyloric and duodenal mucosa and in the juice secreted from these parts of the alimentary canal under the influence of secretin.

II. Clinical part, by JAN WALDENSTRÖM.

The clinical testing of the preparation previously described by Ågren has been carried out on four patients with pernicious anemia at the Medical Clinic of the University Hospital, Uppsala. Three cases suffered from untreated pernicious anemia one case was in a relapse. The result was somewhat varying but in two cases there was seen a very prompt and effective response. The case histories will be briefly related and discussed before I enter on a general discussion of the subject.

Case I. Male patient born in 1864. Admitted on Jan. 17th 1944 because of bad appetite, loss of weight and anemia. The chief features of the blood picture are seen from fig. 1. Tongue absolutely smooth. No neurological
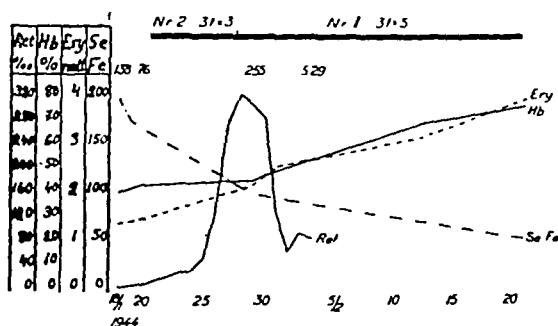
Fig. 1. Graph showing response in a case of pernicious anemia (Case 1) to oral treatment with liver activated with purified aminopolypeptidase.

symptoms. No urobilinuria, but icterus index 11 (Meulengracht). Histamine refractive achlorhydria. White blood cells 7,100. Differential count normal. Considerable anisomacrocytosis. No occult blood in the stools. Roentgen of the stomach: no signs of tumor. Sedimentation reaction 40—50 mm/hour. No fever. Sternal puncture: typical megaloblastic marrow. The patient was observed a few days before treatment, during which time the blood values remained constant. He was then treated with the stronger preparation (Nr. 2) for seven days. When a definite reticulocyte response was found, he was given the preparation number 1. The effect was very good as is seen from the curve. His appetite increased very much. The papillae on the tongue regenerated rapidly. The S.R. went down to 3 mm/hour.

It is obvious that the response was very effective as regards all symptoms. The reticulocyte peak reached the maximal value as defined by Minot for that initial erythrocyte count. The increase of the platelet count was very strong and comparable to the maximal values found by Wal-

denström and Öberg after massive doses of liver extract. The regenera-
tion of the papillae of the tongue was very complete and rapid (registered
photographically). Also the S.R. and the icterus index were restored to
normal. The value of 4 Mill. was reached in practically one month. This
compares well with the averages found by the American authors (Murphy
et al.) after massive parenteral therapy. The response of the serum iron,
which according to Waldenström (1944) is an absolutely reliable sign of a
remission, was also marked. It is to be regretted however that there were
no determinations made before the 8th day of the treatment, as the lowest
value is usually found between the 3rd and 5th days of the treatment (see
Waldenström, 1944).

Case II. Male patient born in 1878. He was first admitted on May 10th
1939 with signs of typical pernicious anemia. Red blood cells 2 mill. Hemo-
globin 58 %. He was treated with Campolon in massive doses and reacted

Fig. 2. Graph showing response in a case of pernicious anemia (Case 2) to oral
treatment with liver activated with purified aminopolypeptidase.

well on this therapy. After two months' treatment the erythrocyte count
was 4.6 mill. Hemoglobin 87 %. In June 1942 he stopped treatment and
came back on Sept. 28th 1943 in a severe relapse. The blood values are seen
from fig. 2. The tongue was absolutely smooth. The patient was put
on a treatment with Tablets number 2 but was allowed to stay at home.
He came to the Policlinic every other day. The reticulocyte peak could
therefore not be definitely established but the rise was less rapid than for
the other patient. The drop in serum iron however was quite typical, the
platelet peak was very high and the erythrocyte count reached 4 mill.
between 3 and 6 weeks after institution of the treatment. The papillae on
the tongue regenerated rapidly (photo) and the general status of the pati-
ent improved considerably.

The treatment was stopped on Nov. 11th and the patient was for
some reason ordered iron tablets by another doctor. During this treatment
the blood count did not change but the papillae on the tongue disappeared
completely (recorded photographically). They reappeared and continued to

be normal after treatment with liver extracts. The previous reaction of the anemia on treatment with liver extracts puts the diagnosis beyond doubt. The effect of the new preparation was not so strong as in Case I. It was very typical however and resulted in a practically complete cure with 4 mill. ery between 3 and 6 weeks after institution.

Case III. Male patient born in 1897. Admitted on Jan. 17th with high fever and signs of pneumonia. The fever soon subsided with sulphathiazol treatment. There were found typical signs of pernicious anemia. Blood values: see curve III. Urobilinuria. Megaloblastic sternal marrow and anisomacrocytosis. Leucocytes 3100/mm³. Differential count normal. The S.R. showed very high values (pneumonia). The result of the treatment on the blood values is seen on fig. 3.

The reticulocyte peak was rather low but still corresponded to the average percentage value determined by Murphy after intramuscular in-
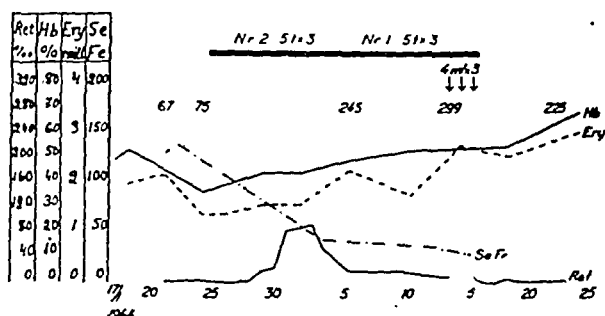
Fig. 3. Graph showing response in a case of pernicious anemia (Case 3) to oral treatment with liver activated with purified aminopolypeptidase.

jection of potent liver extracts. There was found an average platelet peak on the 11th—17th day. The serum iron value was definitely lowered. The increase in the erythrocyte count was slow also after parenteral liver extract (Heptomin 4 ml × 3).

In order to test the potency of the first peroral preparation the patient was later given massive doses of a potent liver extract intramuscularly, but without a second reticulocyte reaction. This ought to be interpreted as a sign that the second dose was not more potent than the first. The serum iron value at the time of the injection was already low and was not materially altered by the injections. There was no second increase in the platelet count.

Case IV. Female patient born in 1880. Clinical picture not quite characteristic for pernicious anemia. Since Nov. 1943 bad appetite, never hungry, often vomiting. Tongue-burn. No fissures in the corners of the mouth. Severe loss of weight. Admitted for anemia and increased S.R. on Jan. 12th. Tongue red, practically smooth (photograph). Normal blood pressure.

Left achilles reflex absent. Urobilinuria, no albuminuria. Sternal puncture: normal marrow, no megaloblasts. White blood cells 5,700. Differential count normal. Roentgen of the stomach normal. Histamine refractive achlorhydria. Price-Jones curve (photographical technique on dry film), determined by dr. K. Möller showed increased mean diameter 8.69 (Normal value 7.64 ∓ 0.165) and anisocytosis ($\sigma = 0.67$ as compared with the normal 0.42 ∓ 0.028). Curve typical for pernicious anemia. N.P.N. 28 mgm %.

The patient was given 30 g raw liver daily as a test dose for 8 days. No reticulocyte response, no platelet increase. No drop in serum iron. She was then given the new preparation Nr. 2. This gave a decided drop in serum iron and a slight reticulocyte peak corresponding to an average increase (Murphy). There was no increase in the platelet count. The erythrocytes increased slowly. Fig. 4

The second reticulocyte response was therefore tested after the administration of large doses of liver extract intramuscularly. There was no
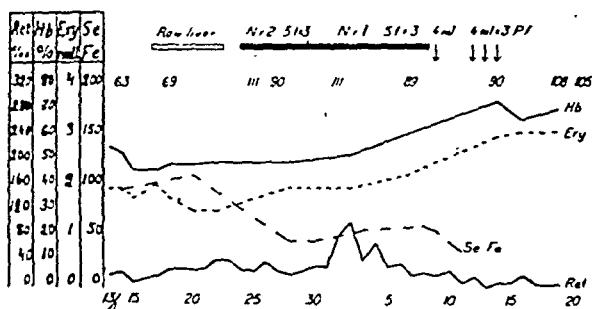
Fig. 4. Graph showing response in a case of pernicious anemia (Case 4) to oral treatmentwith liver activated with purified aminopolypeptidase.

change in reticulocyte or platelet count. The later increase in the erythrocyte count is probably partly due to a delayed action of the peroral preparation. The testing of the second reticulocyte response makes it impossible to judge this question. On the other hand the absence of a second reticulocyte response ought to indicate that the first peroral treatment was not less effective than the second. The decided influence of the liver extract treatment on the serum iron probably shows that it gave a further improvement. There was no platelet increase after liver extract, the regeneration of the lingual papillae was slow and incomplete and the increase in blood values also came very slowly. By some unknown cause the patient must have been somewhat refractive also against otherwise potent liver extracts.

As a comparison the following experiments my be quoted. They were performed to a large part by dr. L. Hallén in order to test the content of intrinsic factor in gastric juice from different patients.

Man born in 1867. Typical pernicious anemia now in relapse. Treated for 8 days with 30 g raw liver. No reticulocyte response. Serum iron: no definite drop. After a pause of two days the patient was given the same amount of liver digested with gastric juice from a person suffering from histamine refractive achlorhydria. There was a very slow increase in reticulocytes with a maximum of 70 $^0/_{00}$. After this treatment a pause for a week. Minimum serum iron value 50 γ %. During this time the serum iron again became high (165 γ %). The patient was again given liver, now digested with normal gastric juice for five days. He got a maximal reticulocyte response of 65 $^0/_{00}$ and a marked drop in serum iron (50 γ % on the 3rd day and 30 γ % on the 7th day). The erythrocytes increased already after the treatment with liver + gastric juice from an achlorhydric person.

Man born in 1876. Typical pernicious anemia. The patient was given 20 g liver digested with 20 ml normal gastric juice for 10 days. With this treatment reticulocyte response of 62 $^0/_{00}$. No drop in serum iron, no platelet crisis. With Campolon good results.

Woman born in 1867. Typical p.a. Treated for 11 days with 20 g digested liver (normal gastric juice). No reticulocyte or platelet response. No drop in serum iron, no increase in erythrocytes. With Campolon good results.

Woman born in 1863. Typical p.a. Treated with 20 g raw liver daily for a week. No reticulocyte reaction, no drop in serum iron. The patient was then given 20 g liver, digested with gastric juice from a patient with gastric anacidity. Serum iron on the 8th day 35 γ %. No reticulocyte reaction, no increase in red cells. Treated with Heptomin without reticulocyte reaction but with good improvement of the blood values.

The clinical examples just quoted seem to show, that liver in the doses of 20—30 g daily in themselves do not have any decided influence on the blood values in untreated pernicious anemia.

When the liver is digested with normal gastric juice for 2 hours at a $P_H = 2$—3 according to Reimann the mixture had a very good effect on the blood values in one case and influenced the serum iron and reticulocyte values in several instances. This is in perfect accordance with the results of Reimann and his school as regards the hematological response. The SeFe has never before been tested in such experiments.

For the present investigation of the influence of a highly puri-
fied preparation of amino-polypeptidase the above — mentioned
experiments are of considerable interest. They show that the in-
fluence of the concentrated enzyme preparation plus liver is more
constant and sometimes much stronger than was the influence of
liver plus gastric juice from achlorhydrics or even of liver digested
with normal gastric juice on the blood values in four cases treated
in this way.

The clinical facts therefore seem to favour the assumption that
a concentration of the aminopolypeptidase increases the activity of
the intrinsic factor. It therefore seems possible that the amino-
polypeptidase may be identical with the intrinsic factor as was
first assumed by Ågren.

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Head: Professor N. Antoni.

Report on two prodigy mental arithmeticians.

By

STIG JAKOBSSON.

During the last two years I had the opportunity of studying two individuals possessing a prodigious ability to do mental arithmetic. One of these, a young girl, Gullan B., aged 21, was under treatment at the Neurological Clinique of the Serafimer Hospital in Stockholm (Record: No 397/42; this case had already been published once before in the Nord. Medicin 1942: 16: 3266); the other a young man, Ingemar G., aged 21, a student of philosophy, came under my observation through an advertisement in the newspaper announcing his phenomenal capacity for arithmetic.

The past history of the young girl and the examination of her condition revealed in brief the following facts. With regard to heredity, there was nothing of interest. Neither her father nor her mother nor any of her brothers and sisters displayed any special talent for arithmetic. When she was about 2 or 3 years old she contracted a trauma of the skull associated with loss of consciousness. As a child she manifested »a nervous twitch» of the arms and the face. According to her statements she had been a good pupil and had at school been considered clever at arithmetic. As long as she could remember she had felt a weakness in her right arm and leg. The somatic examination showed that she was stout and that the belonged to the dysplastic type. The neurological exami-

nation revealed a mild right-sided spastic hemiparesis. She was left-handed.

From the psychological point of view, she appeared to be very childish and somewhat dull. On measuring her intelligence (Wåhlén) the scored 42 out of 50 points, i.e. lower limits of adult age. Owing to the fact that this method gives with regard to mental retardment too high a score a sum of points ranging between 40—45 is usually considered to indicate a slight mental retardment. Her orientation in time and space was satisfactory. Her attention and capacity for concentration were excellent. She passed the 100 — 3 — subtraction test without making any mistakes and required very little time for it. Bourdon's test (i.e. underlining, for instance, certain letters recurring in a text) she passed fairly well too. Her memory was good, though not remarkable. On testing her memory for objects (5) she responded correctly without any mistakes after 3 minutes diversion. She immediately repeated 8 digits, but not more. On testing her ability for associations she passed 9 items out of 10 correctly after 5 minutes diversion. Her memory for incidents of recent occurrence appeared to be intact whereas her recollection for remote occurrences was poor. When questioned about things which happened a few years previously or earlier, she always gave the same answer, namely »That I dont know». As I shall prove later on in this paper, her ability for mental arithmetic was considerably above the mean. She could write simultaneously with both hands from left to right and reverse, upwards and downwards and could do mirror-writing.

The young male prodigy arithmetician was the son of an elementary school teacher. Also in his case the family history failed to elicit that any member of the family or other relative was endowed with any special gift for arithmetic. The grandfather on the father's side was said to have had a »head for figures», but to what extent exactly was not known.

This prodigy arithmetician had attended six classes of an elementary school and had then continued to learn at home, alone with only his father to help him. After 2 years he enrolled in a secondary school (realskola), and at the end of one year at this school he passed his finishing off examination (realexamen). For his paper in mathematics he gained »A» (= excellent), for his »general knowledge» of mathematics »a» (= very good). For three

years he continued to study alone at home, taking only two corres-
pondence courses, namely in Swedish composition and English.
In 1941 he passed his matriculation examination in modern sub-
jects (reallinjen) as a private student choosing as his special sub-
ject mathematics. In mathematics he obtained for his paper »a»
(= very good) and »AB» (= higly satisfactory) for his proficiency
at the oral examination, for history and scripture he obtained »AB»
(= highly satisfactory), for physics, English and Swedish »Ba»
(= very satisfactory), and his proficiency in chemistry and in
Swedish composition as well as his paper in English were appre-
ciated as »B» (= satisfactory). He intended to obtain his B. Sc. in
mathematics, statistics and political economy.

As will be understood by the above reported data, the young
man in question was a gifted and energetic individual. He was
chiefly interested in mathematics for which he was especially gifted.
He stated that he had a good memory and that he belonged to those
whose visual memory is especially pronounced. In a game of
chess, however, he had difficulty in remembering the position of the
chessmen if interrupted, and he had no memory for syllable and
letter absurdities. Thus, it becomes apparent that he had a spe-
cially pronounced memory for figures. He was able immediately
to repeat 10 figures but not more. At school it was his hobby to
learn by heart the number of inhabitants of all the large towns
in the world and he was able to repeat them almost accurately.
Even when attending the second class of the elementary school he
noticed that his ability for mental arithmetic was superior to that
of his schoolfellows and that it gradually grew more and more
pronounced. He reported that when he had nothing else to do, he
multiplied and divided sums, but he did not consider that he de-
voted a great deal of his time to this kind of occupation. But
when he explained his method of procedure, it became apparent
that he had a large reserve of associations with regard to different .
numbers and figures and that these associations helped him in
remembering and repeating them. The figures and numbers may
refer to anything, as for instance to individual weight, size and age,
to sports (to his own achievements as well as to that of others), to
street- and telephone numbers a.s.o.

Arithmetical Problems.

In the following I shall give in tabular form the sums which these phenomena in mental arithmetic did mentally as well as the time required for their solution expressed in seconds. At first I shall state the problems which both of them solved and then a few which only Ingemar G. solved and which doubtless are beyound the young girl's ability. She came under my observation long before I came into touch with the young man and therefore I did no have any opportunity of giving her a trial with these sums. The problems were, of course unknown to them before the test.

	Gullan			Ingemar	
	Answer	Time		Answer	Time
323 + 495 =	818	15	seconds	= 818	immediately
337 + 675 =	1012	20	»	= 1012	»
117 + 693 =	810	27	»	= 810	»
1017 + 3095 =	*4012*	12.4	»	= 4112	»
	correct answer: 4112				
113 − 95 =	18	9.8	»	= 18	»
693 − 207 =	486	12	»	= 486	»
2609 − 713 =	*1996*	28.2	»	= 1896	»
	correct answer: 1896				
7345 − 2074 =	*5369*	41	»	= 5271	»
	correct answer: 5271				
12 × 14 =	168	immediately		= 168	immediately
13 × 17 =	221	»		= 221	»
15 × 18 =	270	»		= 270	»
16 × 19 =	304	»		= 304	»
25 × 27 =	675	»		= 675	»
23 × 29 =	667	5 seconds		= 667	»
16 × 75 =	1200	4 »		= 1200	»
43 × 53 =	2279	7 »		= 2279	»
89 × 95 =	8455	9 »		= 8455	1.5 seconds
17 × 437 =	7429	12 »		= 7429	2 »
237 × 415 =	(no solution obtainable)			(was not given to Ingemar)	
73 × 125 =	9125	immediately		= 9125	immediately
305 × 125 =	38125	»		= 38125	»
1303 × 125 =	162875	»		= 162875	2 seconds
23 × 375 =	8625	4 seconds		(was not given to Ingemar)	

	Gullan			Ingemar	
	Answer	Time		Answer	Time
$279 \times 375 =$	104625	17 seconds		$= 104875$	2 seconds
				correct answer: 104625	
$1139 \times 375 =$	427125	44 »		$= 427125$	5 »
$37^2 =$	1369	5 »		$= 1369$	immediately
$54^2 =$	4096	5 »		$= 4096$	»
$73^2 =$	5329	7 »		$= 5329$	»
$93^2 =$	8649	12 »		$= 8649$	»

$329: 17 =$	19 remainder 6	7 seconds		$=$ 19 remainder 6	immediately
$9215: 16 =$	575 »	15 4 »		$= 575$ »	15 5 seconds
$1745: 103 =$	16 »	97 21 »		$= 16$ »	97 15 »
$6377: 89 =$	(solution not obtainable)			$= 71$ »	58 9.5 »

In the following several arithmetical problems will be reported which were only given to Ingemar G. In doing the addition I read aloud the different items at intervals ranging from 1 to 1.5 seconds. Immediately after I have read aloud the last item he announced the total.

$434 + 617 + 358 + 945 + 263 + 784 + 514 + 129 = 4044$

$342 + 573 + 607 + 981 + 124 + 434 + 769 + 856 + 288 + 327 = 5301$

$23 \times 367 =$	8441	4 seconds	$642 : 18 = 35.666 \ldots$	2 seconds
$65 \times 753 =$	48945	13 »	$5145 : 17 = 302.64705$	5 »
$139 \times 459 =$	63801	10 »	$9046 : 313 = 28.964$	28 »
			correct answer: 28.9009	
$128 \times 354 =$	45312	8 »	$6252 : 45 = 148.9556$	17 »
			correct answer: 138.9333 \ldots	
$344 \times 759 =$	261096	22 »	$3951 : 72 = 54.8888 \ldots$	13 »
			correct answer: 54.875	
$43 \times 6432 =$	276576	13 »	$7842 : 356 = 22.02809$	26 »
$57 \times 3893 =$	335901	34 »	$193863 : 247 =$ (no solution obtainable)	
correct answer: $= 221901$				

$\sqrt{359} = 18.947$	2 seconds		$\sqrt[4]{5432} = 8.707$	13 seconds
			correct answer: 8.781	
$\sqrt{1114} = 33.37$	6 »		$\sqrt[4]{43124} = 14.415$	29 »
$\sqrt{6536} = 80.84$	9 »		$\sqrt[4]{73482} = 16.439$	21 »
			correct answer: 16.455	
$\sqrt{15672} = 125.188$	8 »			
$\sqrt{24105} = 155.257$	11 »			

The above reported examples illustrate that Gullan B. was rather slow at doing addition and substraction and that her answers were relatively often incorrect. Multiplication of numbers of two figures below 30 (for instance 23 by 27) she solved immediately, sometimes, though very rarely, after a very short reaction time. Multiplication of numbers of two fingures by numbers of three figures she also solved very quickly. Multiplication by 125 or numbers commensurable by 125, for instance 375, 500 and 625 a.s.o. she solved very quickly. She squared any number almost as quickly as she did any corresponding multiplication. Consequently, she did not know the square numbers by heart, at least not as far as high numbers were concerned. Division she did with great sureness and rapidity. She did not only state the quotient but also the remainder when there was one. On the other hand, she did not state the decimal figures of the sum total. She could not extract the square root, which, however, may be explained by the fact that she did not know what was meant by it.

Ingemar's ability for doing arithmetical sums was without any doubt superior to that of Gullan's. Not only is he equally good at multiplying, adding, dividing and substracting, but he also did sums with numbers of several figures and required much less time than Gullan did. He also solved sums which Gullan could not solve at all. He added up, for instance, ten numbers of three figures, extracted the square root and the fourth root, divided numbers of 4 figures by numbers of three figures and stated a quotient of up to 5 decimal numbers. He multiplied numbers of two figures by numbers of four figures and numbers of three figures by numbers of three figures but, as a rule, not higher numbers. Gullan multiplied only numbers of 2 figures by numbers of 3 figures with the exception of such numbers as 125, and of products of multiplication by 125.

Method of Procedure in Doing the Sums.

How did they manage to do the sums so quickly? Ingemar B. who was far better in explaining the manner in which he proceeded, gave the best description. The girl made rather a mystery of her ability for doing arithmetical sums. She answered elusively when questioned about her manner of proceding. She had to be forced into describing it.

In doing addition and substraction they did not make use of any abridgements. Their ability to »see» the numbers clearly in their mind's eye was to them a valuable aid. Even if the numbers were given to them orally, they were able to see them in their imagination. »They see the numbers written in the air».

In multiplying low numbers of two figures (for instance 23 × 27) they make use of »extended multiplication Tables», that is to say, multiplication Tables up to 30 by 30. These products as well as several products by higher numbers which had become fixed in their memory, they knew by heart. Otherwise they proceeded in the following manner. They divided the numbers into parts until they had figured out amounts, the products of which they could either easily ascertain or which they knew by heart. Then they added up the items (see ex. 1). This method can be applied to any number.

Ex. 1. $17 \times 437 = 7429$ Explanation:

$$17 \times 400 = 6800$$
$$17 \times 30 = 510$$
$$17 \times 7 = 119$$
$$\overline{\qquad 7429}$$

The young girl did this multiplication which included the adding up of three numbers in a strikingly short time. In general, she required for the adding up of two numbers the same time as she required for this problem. I failed to find an explanation of this fact.

With some multiplications abridgements are applicable. The methods described below were not elaborated by the two individuals reported in this paper, they have long been known and have been described in manuals of instruction for ready reckoning.

If two numbers of the same number of figures are given having a mean the square of which is known, Ingemar G. proceeded in the following manner (see ex. 2 and 3).

Ex. 2. $48 \times 52 = 2496$ Explanation: mean $= 50$

$$48 \times 52 = 50^2 - (50-48)^2$$
$$= 50^2 - 2^2 = 2500 - 4$$
$$= 2496$$

Ex. 3. $78 \times 84 = 6552$ Explanation: mean $= 81$

$$78 \times 84 = 81^2 - 3^2 = 6561 - 9$$
$$= 6552$$

Thus the product is equal to the square of the mean minus the square of the difference between the mean and the multiplier. As was stated above, this method is time-saving only on condition that the square of the mean is known.

If the multiplier is a number in the vicinity of some round number, one proceeds in the following manner (ex. 4 and 5).

Ex. 4. $127 \times 359 = 127 (360—1) = 45720 — 127 = 45593$

Ingemar knew the product of 127×36 »almost by heart».

Ex. 5. $546 \times 784 = 784 (550—4) = 431200—3136 = 428064$

Multiplication by round numbers which are parts without remainders of hundreds, thousands a.s.o. are done in the following manner (see ex. 6 and 7). If the multiplier is 25, the multiplicand is divided by 4 ($= 100 : 25$) and the quota is multiplied by 100, if there is no remainder. If there is a remainder, a remainder amounting to 1 is equal to 25, a remainder amounting to 2 is equal to 50 and a remainder amounting to 3 is equal to 75 which numbers are added to the respective hundreds.

Ex. 6. $25 \times 272 = 6800$

    Explanation: $272 : 4 = 68$ The product to be figured out
                         $= 6800$

Ex. 7. $25 \times 131 = 3275$

    Explanation: $131 : 4 = 32$, remainder $= 3$ (corresponding
                    to 75) The product to be figur-
                    ed out $= 3275$

Multiplication by 125 or by products thereof are, in principal, done in the same manner. 125 being the quota of 1000 divided by 8, the product, when multiplying by 125 as well as by any other number may be figured out by dividing the number by 8 and multiplying the quota (which indicates thousands) by 1000. If there is a remainder, a remainder amounting to 1 is equal to 125, a remainder amounting to 2 is equal to 250, a remainder of 3 is equal to 375 a.s.o. These numbers are added to the respective thousands (ex. 8 and 9).

Ex. 8. $125 \times 728 = 91000$

    Explanation: $728 : 8 = 91$ The product to be figured out
                      $= 91 \times 1000 = 91000$

Ex. 9. $125 \times 575 = 71875$

    Explanation: $575 : 8 = 71$, remainder $= 7$ (corresponding
                  875) The product to be figured
                out $= 71875$.

If one does not wish to learn by heart the different numbers which correspond to the different remainders, one only has to multiply the multiplier by the remainder. Thus, in ex. 9, 7 by 125 = 875. In this manner the young girl proceeded.

Multiplication by 143 affords no difficulty, as 143 = 1001 : 7.

Ex. 10. $143 \times 674 = \dfrac{674 \times 1001}{7} = \dfrac{674674}{7} = 96382$

When squaring Gullan proceeded in the same manner as when doing an ordinary multiplication. Some squares she knew by heart. Ingemar, however, was familiar with the majority of squares of the numbers below 100. He made use of this knowledge when extracting the square root. If he had to extract $\sqrt{6536}$, he knew that the nearest number corresponding to a rounded up square of a round number was 6561 = 81². The difference between 6561 and 6536 is 25. The number which was to be figured out $= 81 - \dfrac{25}{2 \times 81} =$ 81—0.1543 = 80.8457.

$\sqrt[4]{}$ is ascertained by first extracting the square root of a given number, and then extracting the square root of the result.

When doing division Ingemar sometimes used, though comperatively seldom, abridgements (ex. 11 and 12). Otherwise he did division after the routine method.

Ex. 11. 329 : 17 = 19, remainder = 6

    Explanation: he departs from the fact that 324 = 18²
        consequently, 323 = 17 × 19
        thus, 329 : 17 = 19, remainder = 329 — 323
        = 6

Ex. 12. 9215 : 16 = 575, remainder = 15
    Explanation: 9215 = 9200 + 15
    He knows that 9200 is commensurable by 16,
        9200 : 16 = 575
    Thus, 9215 : 16 = 575, remainder = 15.

The young girl even made use of her extraordinary ability to multiply in doing division. She ascertained the number (= the

resulting quota) the product of which when multiplied by the divisor is equal to or approximates the given dividend (ex. 13).

Ex. 13. $329 : 17 = 19$, remainder $= 6$.

Explanation: $17 \times 19 = 323$
$329 - 323 = 6$
The result to be figured out $= 19$, remainder $= 6$

Some data on Prodigy Arithmeticians.

The two cases reported in this paper possessed an extraordinary ability for mental arithmetic. One was a gifted young man who, besides his ability to do mental arithmetic, was also good at higher mathematics and intended to become a mathematician. The other, a young girl, displayed an ability for mental arithmetic which was considerably above the average but otherwise her intelligence was extremely poor. This is nothing unusual. Even feeble-minded individuals may exhibit both a memory for figures and an ability for arithmetic considerably in excess of the norm. At the Ulleråker hospital an imbecile male patient came under my personal observation who could learn 6 numbers of 6 figures written horizontally within a few minutes by heart. He then could repeat them from memory not only horizontally but also vertically. He also knew by heart almost from beginning to end Wernstedt's »Medical Terminology« as well as a reference book giving data about the communities of Sweden, about their inhabitants, their superficial extent, their geographical position a.s.o. Wizel reports the case of a young girl of 22, who was prodigious in mental arithmetic, but who in other respects was very feeble-minded. [1] Normally gifted individuals, as well as feeble-minded ones, seem to exhibit a pronounced memory for figures and words rather than any remarkable ability for doing sums. With regard to mental arithmetic, however, both factors must be present more or less.

Prodigy arithmeticians and »jugglers« with figures have always been objects of general interest, not only because their proficiency is far above the average, but also because they pass for being unusually intelligent. There exist, of course, prodigy arithmeticians, who also may be considered as gifted mathematicians, for instance Rückle who makes use of his theoretical knowledge in doing sums.

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[1] Further data on such cases are available.

Bidder too, was besides a very successful engineer. But among the other phenomena in arithmetic there are only a few who, apart from their prodigious head for figures, display any extraordinary intelligence.

What factors come into play in creating prodigy arithmeticians? Heredity plays a very insignificant part in this process. In the cases in which the ability seemed to be hereditary, it was inherited from the father. Müller, too, does not believe in an innate extraordinarily good memory for figures. In my 2 cases there was no such evidence either. In the opinion of Müller and Binet this superior talent for arithmetic is due to an exceptional ability to concentrate, to a quick conception and to the fact that the individual does not feel any fatigue and to his memory for associations. As — siduous practise, however, seems to be of major importance. The individuals display a keen interest in numbers as well as in their characteristics. This interest is manifested at a tender age already. The prodigy arithmeticians reported in Binet's book, manifested the first indications of a pronounced ability for doing sums as the ages ranging from 3 to 10 years. They devoted their spare time to doing arithmetical problems and thus brought themselves »to see» the numbers in their mind's eye. They also learned a lot of abridgements and tricks which later on were a valuable aid to them. Through constant practise they accumulated an enormous supply of figures and numbers in their memory. It is very interesting to read what Nils Larson states in the preface of his manual of instruction for ready reckoning: »Ever since I was a child I was greatly interested in mental arithmetic; even as a little boy I went to solitary places, avoiding the noisy games of my playmates and devoted myself to my beloved mental arithmetic. I wrote the figures in the air with my finger, multiplied them and tried to ascertain the products. Thus I became a »mathematical visionary» and was able to see invisible products in exactly the same manner as one is able to see in one's mind's eye, one's faraway home where one passed one's childhood, one's native town, one's parents, relatives and friends ... At the age of 9, I was able to say without the help of the queer procedure I had originally devised, namely »writing in the air», quickly and without any mistakes the product of numbers of two figures multiplied by numbers of three figures, in some cases the product of numbers of three figures by numbers of four figures

and even of numbers of four figures multiplied by numbers of five figures ... I had at this stage already discovered all abridgements and tricks by which to do multiplication speedily.» Ingemar B. also reported that he did mental arithmetic in his free time. Mental arithmetic had become a hobby, almost an obsession.

Summary.

The author reports two prodigy arithmeticians. The one is a gifted young man who intends to become a professional mathematician, the other, a young girl, is feeble-minded. Tables are given indicating a comprehensive series of arithmetical examples, the respective reaction times as well as the methods employed in solving the problems.

A great interest in numbers manifested at an early age and constant practise in mental arithmetic from early childhood on, seem to be the psychological factors which play the most important part in creating a prodigy arithmetician. Most individuals possessing a prodigious ability for mental arithmetic, exhibit a pronounced visual memory, a good memory for associations, a rapid conception, a remarkable capacity to concentrate and indefatigability.

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Case of Leukemoid Eosinophilia.

»Eosinophilia Leuchemoides».

By

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(Submitted for publication August 2, 1944.)

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Cases of »eosinophilia leuchemoides» or »eosinophilic leukemia» are relatively rare, only 3 cases of this lesion having been reported so far in the Scandinavian literature (Thomsen & Plum; Engbæk, Heerup & Thomsen; Bang). In lesions with obscure etiology, pathogenesis and even clinical features it is highly important that all cases observed be described and recorded as thoroughly as possible. On this account I shall here report a case I have had an opportunity to observe. As the literature on the lesion and appertaining problems have been reviewed and discussed thoroughly in the aforementioned paper by Engbæk, Heerup & Thomsen, I shall not here enter into these questions except to the extent required for discussing my own case and otherwise refer the interested reader to the previous paper mentioned.

Case Record.

The patient was a painter, 37 years old. (Reg. No. 486/42).

The family history was negative as to allergic diseases; and he gave a past history of good health except for a couple of minor surgical affections.

Present Illness. — Since December 1941 the patient had been suffering from dyspepsia as manifested by poor appetite, 3—4 thin stools daily,

colicky pains after the meals throughout the abdomen, and borborygmus. He has not noticed any mucus or blood in the stools. In the latter part of January 1942 he was confined to bed for 10 days on account of »influenza«. After this he felt very tired but kept attending to his work till 23/3/1942, when he again had »influenza« with fever, cough, marked tiredness, and profuse sweating, but no pain or expectoration.

On 7/4/1942 he was admitted to this department. He was then pale, sweating, but not cyanotic or dyspneic. The liver extended 3 fingers', breadth below the costal margin. The spleen was not palpable. A moderate degree of ascites was ascertained. No palpable enlargement of the lymph glands in the neck, axilla or inguen. No petechiae or ecchymoses. Gums normal. No other abnormality revealed by the physical examination.

He stayed in this department for ten weeks (till 18/6). During this period his general condition was somewhat variable but ultimately he improved a little. He presented no other particular symptoms but a transitory paresis of the right facial nerve from cold. The liver increased somewhat in size, reaching the umbilical transversal at the discharge of the patient. The temperature was subfebrile during his stay in the hospital, except for a period during which it was more oscillating, rising up to 39.8° C.

Laboratory Examinations. — Urine: + albumin (0.1—0.5 %) otherwise no pathological elements (especially, no microscopic hematuria). Wassermann negative. Blood pressure 115/70. Blood grouping: A. Feces: 0 blood, 0 eggs of parasites, 0 parasites. Roentgenography of the lungs, heart, and proximal ends of the long bones: No abnormality. Widal negative. Gonoreaction negative. Echinococcus complement fixation tests negative. Blood urea 21 mg %. Urea clearance normal. Plasma color (Meulengracht) 9 and 7. Takata-Ara: +++ (repeatedly). Hemoglobin (Sahli): 81, 84, 85, 90, 83, 78 and 81 %. Sedimentation test: 93, 96, 77, 107, 126 mm/hr. Thrombocytes: 52,800. Serum protein: 8.2 %. Serum calcium: 8.9 mg %. Formalin gel reaction: + (less than 3 min).

The peripheral blood showed moderate leucocytosis with marked, constant eosinophilia (see description below). On this account a test for hypersensitiveness was performed ad modum Krainick (intracutaneous injection of his own blood diluted) with the result: No hypersensitiveness. In addition, patch tests were made with 22 different substitute dyes and lacquers, all with negative results. Sternal punctures showed marked eosinophilia (see description below). Biopsy of the liver showed eosinophil infiltrations of the increased periportal connective tissue (see description below).

After his *discharge* from the hospital he returned frequently for control examination. The peripheral blood presented no changes whatever, but his condition was rapidly getting worse. He complained of pronounced tiredness and frequent attacks of colicky pains in the abdomen. The liver kept getting larger gradually; and now the spleen could also be felt as enlarged.

Readmission on 23/11/42. Now he was greatly emaciated. The liver extended to the anterior superior iliac crest. The spleen appeared considerably enlarged but could not be defined on account of meteorism. Mode-

rate degree of ascites. Tongue fissured; gums slightly bleeding, somewhat inflamed. Small hard lymph glands were felt on the right side of the neck, in the right axilla and in both groins; they were freely movable and indolent. His condition was gradually getting worse, and he died on 24/12/42, one year after the onset of the present illness.

Laboratory Examinations. — Urine: + albumin (about 1—1.5 %/00); 0 urobilin (1/10); + urobilinogen. Diastase value normal. Takata-Ara +++. Sedimentation test: 124, 138, 135 mm/hr. Hemoglobin (Sahli): 74, 73, 72 %. Plasma color (Meulengracht): 36. Bleeding time (ad modum Duke): 5 min. Capillary resistance test: 15 petechiae. Prothrombin time normal. Thrombocytes: 16,000; 16,000. Formalin gel reaction: + (less than 1 min.). Serum protein 9 %. Most of the time the temperature was oscillating widely. The peripheral blood and sternal bone marrow showed the same features as before.

Peripheral Blood. — Samples of the blood showed a varying leucocytosis with pronounced and constant eosinophilia. The white blood count varied between 33,600 and 9,300, while the number of eosinophils varied between 27,000 and 4,000. The blood picture presented no particular abnormality beyond the eosinophilia. The eosinophils showed a picture which quite corresponds to the one described, among others, by Thomsen & Plum and by Bang. The eosinophils were fully mature leucocytes and many of them showed a strikingly small number of granules so that smaller or larger parts of the protoplasm of the individual cells were entirely free from granules. In several of the cells the protoplasm was strikingly basophil. In several of the cells the nuclei were abnormal: annular, and also clover leaf-shaped. During the progress of the disease there was an increase in the above-mentioned scarcity of eosinophil granules, whereas the basophilia of the protoplasm was not increased noticeably.

Sternal Bone Marrow, 20/5. — The specimen is very rich in cells, and eosinophils are very predominant, mostly at the expense of the neutrophils, as the erythropoietic cells appear to be present in normal number. The neutrophils and the erythropoietic cells present no morphological abnormality nor any abnormal feature in their mutual proportions. The distribution of the cells is as follows:

	%		%
Myeloblasts	0.8	Monocytes	2.2
Promyelocytes	0.8	Plasma cells	3.2
Myelocytes, neutrophil	7.4	Lymphocytes	5.8
» eosinophil	12.0	Proerythroblasts	1.2
Metamyelocytes, neutr.	12.6	Erythroblasts	7.4
» eosin.	12.8	Normoblasts	10.0
Staff nuclears, neutr.	9.4	Reticulum cells	0.6
Segment-nuclears, neutr.	2.2	Uncharacteristic	0.4
» » eosin.	11.2	Megakaryocytes, normal number	

Here it should be mentioned that the relative frequency of plasma cells was increased as the normal value for plasma cells in the sternal punc-

tate of a subject in the same age-class as this patient is about 1 % (Malthe Jacobsen). — Further, the eosinophils present the same features as has been observed in previous cases: a shift in the proportion of maturity between the protoplasm and the nucleus, as several metamyelocytes are found to present the distinct, dark blue granules, which by most investigators are looked upon as the precursors of the eosinophil granules, and which normally are found only in the most immature myelocytes. As to basophilia and scarcity of granules, the cells of the bone marrow are quite similar to those seen in the peripheral blood..None of the »stem cells« described by Thomsen & Plum are encountered. Thus the eosinophil cells make up altogether 36 % of all the nucleated cells in the bone marrow. Still, it would hardly be proper to speak of any relative shift towards the left in the blood picture and no leukemic hyatus at all.

Sternal puncture was repeated on 27/11, and it showed perfectly analogous features as to the morphology and differential count of the cells. This time the eosinophils made up 27 % of the total number of nucleated cells.

Biopsy of the Liver. — This was performed on 23/5. The report on the examination (Dr. J. Vesterdal Jørgensen) is as follows: The specimen contains several small but, unfortunately, rather markedly contused fragments of liver tissue. In sections of these fragments the periportal connective tissue is particularly conspicuous and filled with cells which almost exclusively are eosinophil. Most of them look like normal leucocytes with a bilobar nucleus, but a smaller number of the cells contain a single round nucleus. There appears not to be any eosinophil myelocytes. Between the eosinophil cells, several reticulum cells are seen. The periportal connective tissue sends numerous irregular offshoots out into the liver parenchyma which is suppressed so that larger amounts of liver tissue gradually are destroyed. Several liver cells show degenerative changes. Here and there an increased number of eosinophils in the sinuses appears to occur in the parenchyma. So here we meet with changes of the same character as have been described in many cases of eosinophilic leukemia; at the same time, these processes appear to have a tendency towards cirrhosis, but this has not developed sufficiently for such a diagnosis.

Autopsy (25/12/42). — The body is greatly emaciated. There is a considerable amount of fluid in the thoracic cavity (about 1 liter). The parietal and visceral pleurae are covered with fibrinous exsudate. The lungs are heavy but apparently not really pneumonic. — The pericardium and heart present no particular abnormalities, especially no parietal thrombi or distinct fibrosis of the myocardium. The liver is markedly enlarged, measuring 34 × 24 × 12 cm.; consistency friable; cut surface showing a distinct nutmeg pattern. Spleen enlarged, 16 × 8 × 4 cm., of firm consistency with distinct follicular pattern in the cut surface. Kidneys of normal size; the capsule is loosened readily; on the cut surface the pattern of the parenchyma is somewhat effaced. The stomach and intestines show rather marked cadaverosis but otherwise no particular abnormality.

Histological Examination (Dr. J. Vesterdal Jørgensen). — Sections

from the *bone marrow* of the sternum and the vertebra show quite uniform pictures. The marrow is markedly hyperplastic; no fat cells are seen at all. Most of the tissue is well preserved but areas of necrobiosis are seen here and there. In addition, there seems to be a moderate hyperemia. Mega-caryocytes are scanty and often degenerated, with acidophil protoplasm and pyknotic nuclei. Apparently there is a moderate increase in the num-ber of hemocytoblasts. The hyperplasia is due to an enormous increase in eosinophil myelocytes and their various stages of development to uni-cellular or bi- or trilobar eosinophils. The production of normal neutrophils appears to be decreased. The same applies to the erythropoiesis but characteristic nests of erythroblasts are still easy to find. Finally, the bone marrow presents a not inconsiderable number of plasma cells and a few lympho-cytes.

Sections from *lymph glands* show hyperplasia, with formation of a loose reticular tissue in which numerous lymphocytes are seen together with several plasma cells and some, but not very many, eosinophil leuco-cytes, the greater majority of which are mature, while some metamyelo-cytes are seen too, besides a few mitotic figures.

Sections from the *spleen* show a good preservation of the structure. The follicles are present in normal amounts, and they are of normal size. The germinating centers show a large amount of detritus from kariolysis. Numerous mature eosinophil leucocytes are found along the blood vessels, whereas such elements are not represented particularly strongly in the red pulp, which presents merely splenocytes, lymphocytes and several plasma cells, the latter often in a considerable number. There is no sign of myelo-poiesis; in particular, nothing is seen that may be interpreted as precursors of eosinophil leucocytes.

Sections from the *liver* show a very marked congestion, occupying the inner half of the acini, as it looks as if the parenchyma has disappeared between the network meshes, leaving merely the outline of the central vein and the Kupffer cells in the walls of the sinuses. All the rest of the section is made up of blood, around which there is a zone of narrowed trabeculae of liver cells and dilated sinuses; and most peripherally there is a narrow rim of relatively normal liver tissue. In this liver tissue multinuclear cells are frequent, affording evidence of efforts at regeneration. Outside this zone the periportal connective tissue is increased, forming a rather dense tissue of rather broad streaks, up to one-third of the width of the acinus. This increase in width is due only to a slight extent to the presence of fibro-blasts, but mostly to a looser reticular tissue with numerous lymphocytes, plasma cells and mature eosinophil leucocytes. Under the proliferation of this tissue the portal veins appear to be narrowed throughout, and in a few places they are difficult to find even where the bile duct and the artery are seen to be sectioned transversally. It has not been possible to demonstrate any definite endophlebitic processes; but, on the other hand, it cannot be excluded that the narrowing of the portal veins may be due in part to reactions in the wall of the blood vessels itself. Myelopoiesis is not observed.

Sections from the *kidney* show no definite abnormality in the glomeruli or tubules, apart from homogeneous eosinophilstaining casts here and there. The blood vessels of medium size are surrounded by a moderate development of reticular tissue of the same appearance as the one described above in the Liver, though with a relatively smaller number of eosinophil leucocytes. Here and there in such areas small arteries are seen with lamellated walls, slightly infiltrated with cells and undergoing fibrinoid transformation. In one larger artery (interlobular) the lumen is almost completely obliterated by proliferating loose connective tissue with mononuclear and polynuclear leucocytes, several of which are eosinophils. There is no cellular infiltration of the muscularis, and only very slight infiltration of the adventitia. Hence, it seems more likely that here we are dealing with infiltrating thrombi than with an instance of endarteriitis. A few veins present recent thrombi, partly containing lumps of bacteria (coccoid rods, in pairs, or in chains). Other thrombi are a little older, but have not yet undergone organization.

In section from the *lung* the bronchi appear normal, especially without the reactions characteristic of asthma. Nearly every section shows congestion, oedema and hemorrhages together with detachment of septal cells and emigration of a few mono- and polynuclear leucocytes. Some blood vessels show leucostasis, and it is noticed that only very few of these cells are eosinophils, whereas the greater part is made up of neutrophil leucocytes. On the other hand, a moderate number of eosinophil leucocytes are scattered throughout the lung tissue. There is no evidence of allergic vascular changes; on the other hand, a few small vessels show small simple fibrinous thrombi.

Apart from the findings in the bone marrow, all the reactions here observed give the impression of being more reactive than systematically proliferative.

Microscopic Diagnosis: Hyperplasia of the bone marrow (as in the so-called eosinophilic leukemia); Hyperplasia of lymph glands (increase in eosinophil leucocytes and plasma cells); Hyperplasia of the spleen; Cirrhosis of the liver, incipient; Chronic passive congestion of the liver; Infiltrations of the liver and kidneys; Thrombosis of renal veins; Organized embolism of the interlobular renal artery; (Sporadic hyperergic-allergic reactions of a few small renal arteries); Congestion, oedema and hemorrhage of the lungs; (Bacteriemia).

Epicrisis. This is the case of a man, 37 years old, whose illness lasted about one year. It commenced with dyspepsia in the form of pain after meals, borborygmus, and thin stools. Later the morbid picture was further stamped by oscillating temperature, increasing debility and a gradually marked enlargement of the liver. The spleen and lymph glands were enlarged to a lesser extent. The hemoglobin percentage (Sahli) was falling but on the whole de-

creased but slightly (about 80—70 %). The sedimentation rate was markedly increased throughout the period, with a tendency to a gradual rise. The formalin gel reaction was strongly positive. The thrombocyte count was low, and a latent hemorrhagic diathesis could be demonstrated. The peripheral blood presented a very pronounced eosinophilia, in which the eosinophil cells were slightly atypical, though without presenting truly immature forms. Also the sternal bone marrow showed marked eosinophilia with an increase in all the maturing stages, but without a leukemic hiatus. Biopsy of the liver showed a rather marked eosinophil infiltration. Autopsy revealed a very marked enlargement of the liver and moderate enlargement of the spleen, but otherwise no particular changes. Histological examination showed intense infiltration of the bone marrow, liver, spleen and, in a lesser degree, lymphglands with eosinophil leucocytes. No changes are seen of the character generally required in cases of leukemia.

Discussion.

The salient point in the interpretation of cases of this kind is whether they are to be looked upon as instances of true leukemia or as cases in which the feature of eosinophilia is so pronounced as to make them look like leukemia. In order to recognize a case as leukemia, Engbæk, Heerup & Thomsen insist upon the presence of changes in the organs in keeping with the usual findings in cases of leukemia. According to their studies, only two out of the 14 cases described in the literature will substantiate such a finding. In several of the remaining cases there were signs of allergy even though no allergen could be demonstrated.

In the case here described, as mentioned, none of the changes in the organs characteristic of leukemia were found. There was a pronounced eosinophilia of the bone marrow, but no shift to the left in the blood picture. In the liver and, in a lesser degree, in the spleen, lymph glands, lungs and kidneys, eosinophil infiltrations were seen, but they did not present any really leukemic picture. On the other hand, certain characteristic allergic changes could not be demonstrated — in particular the endarteriitis described by

Engbæk, Heerup & Thomsen — at any rate, if present, such chan-
ges have been merely slightly suggestive.

In spite of a thorough search it was not practicable to demon-
strate any allergen.

If we were to attempt to advance any hypothesis about the
possible etiology and pathogenesis in the present case, it would
not seem unreasonable to pay particular attention to the fact that
in this case the first complaints of the patient consisted in per-
sistent dyspepsia with attacks of diarrhea — symptoms which
persisted throughout the course of this case and varied but little
in intensity. Perhaps the possibility might be conceivable that an
intestinal affection might have given rise to defective digestion
and abnormal intestinal absorption, so that substances might have
been absorbed that really had a toxic effect, so that the organism
reacted hereto with eosinophilia. In favor of this hypothesis one
might perhaps point out that evidently the liver was attacked
early and most severely; furthermore, that the histological picture
of the liver biopsy resembles mostly that of hepatosis, even
though it cannot be said to be quite characteristic. — In this
connection it is to be mentioned that the patient was treated
periodically with diatetic measures, at first without meat, later
without milk, and that these measures did not have the slightest
effect on his dyspepsia or general condition.

Jens Bang objects to the fact that now, while we are still in
doubt as to the etiology and pathogenesis of these cases, we try
to distinguish between leukemia and leukemic eosinophilia, and
he thinks that for the present we should be content to employ
the designation »eosinophilic leukemia». This view may be correct,
perhaps. But then it seems rather strange to select the term leu-
kemia when it looks as if in these cases we are not dealing precisely
with a leukemia, but rather with a lesion of a different nature, per-
haps allergic. For, indeed, we do not designate every pronounced
leucocytosis as leukemic! The fact that the clinical picture of the
lesion may resemble an acute or subchronic leukemia and that all
the cases described so far have terminated fatally is still to be
characterized as a rather unspecific criterion. An important point, I
think, is that the eosinophil leucocytes in the blood present no
leukemic changes proper, but changes comparable to those toxic
changes in the neutrophils as are well-known in cases with marked

leucocytosis. Furthermore, the bone marrow shows no other changes than may readily be attributed to a general hyperproduction of eosinophils, as there is no definite shift to the left. So the designation »eosinophilia leuchemoides» appears for the present to be the most proper and non-committing. Something different, of course, is encountered in the few cases presenting a greater resemblance to leukemia — c. g., the case described by Thomsen & Plum. For in such cases no diagnosis other than leukemia would seem proper.

It appears, then, as if we here are faced by a lesion whose final elucidation is intimately associated with the solution of the many problems offered by the eosinophil cells, the problems of allergy and the puzzle of leukemia itself.

Summary.

Report is given of a case fitting into the nosographical group of »eosinophilic leukemia» or »eosinophilia leuchemoides».

The principal symptoms were chronic dyspepsia with diarrhea and colic, besides gradually increasing enlargement of the liver and emaciation. The peripheral blood and sternal bone marrow showed marked eosinophilia. Autopsy revealed eosinophilic infiltration of the liver, spleen, bone marrow, lymph glands and, in part, the kidneys too. But neither the blood, sternal punctate or tissues presented any true leukemic picture, on which account the author thinks that this may have been an instance of leukemic eosinophilia or »eosinophilia leuchemoides». No allergen could be demonstrated.

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From the Medical Out-patient Clinic (Professor Eggert Møller, M. D.)
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The Direct Diazo Reaction (Hijmans van den Bergh) and Its Clinical Significance Investigated by Quantitative Measurements.

By

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(Submitted for publication May 12, 1944).

The so-called direct diazo reaction in serum has been subject
to considerable discussion, and its clinical significance is by no
means definitively established; as there hitherto has not been
any reliable method for quantitative determination of the direct
reaction at disposal, this is easily understood. By modification of
Jendrassik & Gróf's (1938) method for determination of the total
serum bilirubin (cf. With, 1943, a, c, d) the author has succeeded
in working-out a method for quantitative determination of the
direct diazo reaction (cf. With, 1943, b); this method and some
measurements performed with this technique are given below as
well as a review of the present state of our knowledge about the
nature of the direct diazo reaction.

The Nature of the Direct Diazo Reaction.

The terms direct and indirect diazo reaction were introduced by v. d.
Bergh & Muller (1916) who found that aqueous solutions of bilirubin alkali
did not give any diazo reaction, while this was the case if certain substan-

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ces, e. g., alcohol or bile acids were added to the solution. Bile was found
to give the reaction instantaneously without any addition, and also most
icteric sera gave the reaction, the majority however first after a couple of
minutes. The color of the reaction is either clear red or of a more violet
tint changing with the concentration. Reactions taking place without any
addition are called »direct», those taking place only after additions »indi-
rect».

Why bilirubin in some cases shows direct reaction and in others indirect
has been discussed by many authors since v. d. Bergh's original investiga-
tions. V. d. Bergh and co-workers found the indirect reaction in bilirubin-
containing transudates and exudates, in horse serum (very rich in bilirubin)
and in serum from patients with hemolytic jaundice (the hereditary form,
pernicious anemia, paroxysmal hemoglobinuria). In cases of occlusive
jaundice they found direct reaction — and here it has to be remembered
that at this time the acute hepatitis (catarrhal jaundice) was regarded as
occlusive jaundice — and the same was the case in some cases of jaun-
dice following cardiac insufficiency. They discussed the following pos-
sibilities: The presence of two different bilirubin modifications; differences
in the combining of the bilirubin with the serum proteins; variation in the
presence of substances which accelerate or inhibit the reaction in serum;
but they did not arrive at any final conclusion.

Feigel & Querner (1919) further investigated the different reaction
types and used the terms prompt direct, delayed direct and biphasic reac-
tion, the latter in cases with a part of the color appearing immediately
and the rest more gradually.

Lepehne (1920) advanced the hypothesis that only bilirubin which
had passed the barrier of the liver cells gave direct reaction, while circu-
lating bilirubin which had not passed the liver cells reacted but indirectly.
He was led to this belief by the fact that the bilirubin of the bile and serum
bilirubin in occlusive jaundice gives the direct reaction while the serum bili-
rubin in hemolytic jaundice gives only the indirect reaction. Since then
the direct reaction has played a considerable rôle in the differentiation of
hemolytic jaundice from »regurgitation jaundice» (i.e., jaundice with regur-
gitation of bile into the blood; cf. Rich, 1930). Recently, however, Geb-
hardt (1939) has proved experimentally that the hypothesis of Lepehne
cannot be correct, as in experiments on dogs under certain conditions he
only found indirectly reacting bilirubin in the bile, and Pavel (Les Ictères,
Bucarest. 1943, 2. Ed. p. 43) has pointed out that the occurrence of
direct reacting bilirubin in the serum in cases of acute yellow atrophy
of the liver speaks against Lepehne's hypothesis, as in this condition
the liver cells are necrotic and the bilirubin of the serum cannot have
passed through them.

Harrop & Barron (1929) found — contrary to v. d. Bergh & Muller —
that carefully neutralized (to the pH of serum) solutions of bilirubin alkali
showed direct reaction and that addition of great amounts of bilirubin
solution to serum resulted in solutions giving the direct reaction. They
were of the opinion that the part of the serum bilirubin showing indirect

reaction was bound to the serum protein while the part showing direct reaction was free; the action of alcohol and bile acids was explained as a dissolution of the protein-bilirubin linkage. In a later paper Barron (1931) expresses the view that the bilirubin formed by the disintegration of hemoglobin is bound to the albumin-like protein globin which is set free as a result of the same process.

Heilmeyer & Krebs (1930) found that the absorption spectra of the direct and the indirect diazo reaction are identical, a fact pointing against the theory of two different bilirubin modifications.

By the investigations of Bennhold (1932) and Snapper & Bendien (1931, 1938) it was shown — by kataphoresis and ultrafiltration — that all the bilirubin in serum is bound to the serum albumins. This fundamental fact has hitherto by no means been known universally in spite of its confirmation by Pedersen & Waldenström (1937). These authors were able to reproduce the findings of Bennhold and, further, found that in the ultracentrifuge all the plasma bilirubin followed the albumin fraction. If a watery solution of bilirubin alkali was added to a solution of serum albumin a linkage between the bilirubin and the albumin immediately took place, but if ovalbumin was used instead of serum albumin no binding took place. Pedersen & Waldenström also discuss the possibility of the combining of serum bilirubin with globin, and they arrive at the result that such a binding is not very likely as the isoelectric point of the artificially produced serum albumin-bilirubin is ca. pH 4.8, showing a good agreement with the protein-bilirubin compound found in serum, while the isoelectric point of a globin-bilirubin compound is to be expected to be found with far more alkalic values. They did not perform direct experiments with artificial globin-bilirubin as they had no pure globin preparation at their disposal.

Polonowski et al. (1942), however, claim that »indirect« bilirubin is bound to globin while »direct« bilirubin is bound to serum albumin. They mixed solutions of bilirubin alkali with solutions of globin or serum albumin and found the bilirubin-serum-albumin giving the direct reaction, while the bilirubin-globin reacted indirectly. Further, the bilirubin albumin solution was difficult to extract with chloroform (only a few per cent of the bilirubin extracted), while the bilirubin-globin solution was easily extracted with chloroform (about 50 % extracted). In agreement with these findings it was found that about 60 % of the serum bilirubin could be extracted with chloroform in cases of hemolytic jaundice but only a few per cent in cases of occlusive jaundice. The bilirubin in transudates and exudates and xanthochrome spinal fluid behaved as bilirubin in serum from hemolytic jaundice. Bilirubin in alkalic solution added to serum from hemolytic jaundice behaved as the bilirubin naturally present in the serum, and the same was the case with bilirubin added to serum from occlusive jaundice. Bilirubin added to pure solutions of serum globulin showed direct reaction and was easily extracted with chloroform.

Kerppola & Leikola (1931) and Kerppola (1936, 1942) have also shown that the serum bilirubin in hemolytic jaundice is far more easily extracted with chloroform than is the case in other forms of jaundice. They give,

however, the explanation that the easily extractable bilirubin is free while the bilirubin more difficult to extract is found as alkali salt. As, after the investigations cited above, it seems to be proved that all serum bilirubin is protein-bound, this hypothesis is of minor interest.

According to Coolidge (1940) the hypothesis of two different modifications of bilirubin, one with indirect and one with direct reaction, is now abandoned. In this connection it is, by the way, to be remembered that there is a possibility of two isomer modifications of bilirubin; so Fowweather (1932) reckons with a keto-enol-tautomeria on the basis of the structural formula of bilirubin, and Halbach (1938) also thinks this to be possible. The real existence or non-existence of these bilirubin modifications cannot be finally investigated before the total synthesis of bilirubin is possible. Further, Coolidge has shown that the effect of alcohol, caffein etc. on the diazo reaction is purely catalytic; the reaction in serum does not seem to depend on the presence or absence of such catalytic substances but on differences in the binding of the bilirubin to the serum proteins. That the action of alcohol is catalytic was demonstrated by evaporating the alcohol after which the same indirect reaction as before the addition of alcohol was found.

The Clinical Significance of the Direct Diazo Reaction.

Also the clinical evaluation of the direct reaction has been subject to discussion.

Some authors reckon with several different reaction types; e.g., Watson (1937) employs the following terms: »direct prompt» (all color developing within one minute); »biphasic prompt» (more than 50 % of the color developing within one minute); »biphasic delayed» (more than 50 % developing after one minute); »delayed» (all the color developing after the first minute); »indirect» (no color without addition of alcohol). His clinical material however, does not support the usefulness of the application of all these different reaction types.

Miller & Machella (1940) write rather vaguely concerning the direct diazo reaction: »it frequently aids in the differential diagnosis of the several types of jaundice» without giving more detailed facts. On the other hand Cantarow et al. (1940) states: »In the presence of hyperbilirubin-emia little or no clinical significance is attached at the present time to the qualitative van den Bergh reaction, except in the diagnosis of hemolytic jaundice».

In this connection it is also to be mentioned that some authors have

ascribed significance to the reaction type of the serum bilirubin with regard to the excretion of bilirubin with the urine. This view, however, does not seem to be correct — as pointed out in a recent paper by the author (With, 1943, c). Also on the theoretical interpretation of the various forms of jaundice the direct reaction has had a good deal of influence. Thus Rich (1930) regards the jaundice of hepatitis (catarrhal jaundice) as a »regurgitation jaundice« because the direct reaction most often is found in this type of jaundice; it seems much more natural to assume that the jaundice in hepatitis is a combination of »retention jaundice« — caused by the inability of the damaged liver cells to transport the plasma bilirubin into the bile — and »lymphogenous jaundice« — caused by the derangement of the liver parenchyma with destruction of the bile capillaries which is known to take place even in mild cases of hepatitis after modern observations with liver biopsy — (cf. With, 1944).

It is to be emphasized that v. d. Bergh himself was very cautious in his conclusions concerning the clinical and physiological significance of the direct reaction. It is the interpretations of subsequent authors which have laid more stress on this reaction than can stand a critical revision.

While the common qualitative direct diazo reaction seems without greater interest in clinical practice, the possibility rests that quantitative measurements of the reaction could yield valuable information.

Quantitative Measurement of the Direct Diazo Reaction.

Concerning the quantitative measurement of the total diazo reaction of serum bilirubin the reader is referred to earlier papers by the author (With, 1942, 1943, a and d). When the reading of the direct reaction is aimed at, the same procedure is used except for omission of the reaction catalysator (*i.e.*, the caffeine buffer). As the color of the direct reaction develops gradually while the total diazo reaction is read fully developed the reading becomes somewhat difficult, as will always be the case with a color which is not constant (if one does not use a photoelectric instrument). By adding alkali to the reaction mixture, however, it is possible to interrupt the progress of the reaction at any time and read the color produced up to that time. The method of Jendrassik & Gróf (1938) is used with the modification that distilled water is employed instead of the caffeine-solution, and the alkalic buffer solution is added at the time when the reaction is to be read (With, 1943, b). If sufficient serum is available it is possible to determine the direct reaction at several times, *e.g.*, ½, 1, 2, 5 and 10 minutes after the

addition of the diazo reagent and thus plot a graph illustrating the course of the reaction (With, 1943, b). Malloy & Evelyn (1938) proposed to read after 10, 30, 60 and 120 minutes; with their method, however, the course of the reaction is not interrupted, and the dilution is so great that the reading of the weak initial colors of the reaction becomes inaccurate; their method is thus not very suitable for the reading of the direct reaction.

As the direct reaction is most commonly read after 30 seconds this reaction time has been used; further readings after 5 and 30 minutes were performed as in Cantarow *et al* (1940) investigations with Malloy & Evelyn's method. The technique was as follows:

0.1 ml serum is placed in each of 6 microtest-tubes (ca. 40 mm in length, inner diameter ca. 9 mm.), and 0.2 ml distilled water is added to 4 of them. To one, acting as control solution, 0.05 ml of »diazo blank» and 0.15 ml alkalic buffer are added, and to the three others 0.05 ml diazo mixture is added with thorough mixing. The time of the addition is noted, and 30 sec., 5 min. and 30 min. later 0.15 ml of the alkalic buffer is added to one of the three glasses. The 30 sec. reaction has to be completed separately as even small variations in time are significant in this case while the two others can be begun at the same time. The three solutions are read in the Pulfrich photometer by filter S. 61 in »Kleinkyvetten» of 1 cm layer of thickness, with the control solution in the other cuvette (same control solution for all three). The remaining two serum samples are used to determine the total serum bilirubin; to one is added 0.2 ml caffeine reagent and 0.05 ml diazo mixture and then mixed; 10 minutes later 0.15 ml alkaline buffer solution is added. To the other the same procedure is repeated with 0.05 ml »diazo blank» instead of diazo mixture. The first solution is then read with the second as control (in the other cuvette).

Reagents: Caffeine reagent consists of 20 g caffeine, 30 g sodium benzoate and 50 g of sodium acetate dissolved in water and diluted to 400 ml. *Diazo blank:* 15 ml conc. hydrochloric acid in 1 l: distilled water. *Diazo mixture:* prepared each time by mixing 0.25 ml (6 drops) of a 0.5 % solution of sodium nitrite with 10 ml of a solution containing 5 g sulfanilic acid and 15 ml concentrated hydrochloric acid diluted to 1 l. *Alkaline buffer solution:* 10 g sodium hydroxyde and 35 g potassium-sodium tartrate diluted to 100 ml.

The »concentration of direct bilirubin» is calculated by the formula $c = 5.32 \times e$ (c in mg per 100 ml; e is the extinction in 1 cm layer of thickness); the concentration of the total bilirubin is calculated from the formula $c = 5.32 (e - k)$; k is a constant determined by the diazo reaction of the caffeine and is about 0.010. It is determined for each set of reagents by mixing 2 ml caffeine reagent, 1 ml distilled water and 0.5 ml diazo reagent and after 10 minutes adding 1.5 ml alkaline buffer solution; reading in 5 cm »Kleinkyvette» by S. 61. The reading divided by 5 gives k.

In icteric sera dilution (1: 5—1: 20) before the performance of the reaction is often necessary to allow accurate photometric reading of the total diazo reaction; as the direct reaction often is weaker than the total, it may be convenient to use greater dilution in the determination of the total than of the direct reaction. The calculated concentrations in such cases are to be multiplied by the respective dilutions before being compared.

The direct reaction thus found is expressed in mg bilirubin per 100 ml serum; by comparison with the total bilirubin it can be expressed as per cent of the total bilirubin.

The method described is identical with that previously published by the author (With, 1943, b) with the exception that distilled water is used instead of the 3/4-saturated solution of sodium acetate; as this solution shows a certain catalytic action on the diazo reaction the values determined by using it were somewhat too high, for which reason it had to be replaced by distilled water.

Previous Clinical Investigations with Quantitative Determinations of the Direct Reaction.

Malloy & Evelyn (1938) mention that they have carried out clinical investigations with their method which *will be discussed elsewhere*; it has, however, not been possible for the author to find any publications containing this discussion. Cantarow *et al.* (1940), using Malloy & Evelyn's method, found in 37 patients without liver disease a direct reaction — measured in per cent of the total bilirubin — from 12 to 50 % after 5 minutes and from 25 to 75 % after 30 minutes; the values were impossible to read in a number of cases with serum bilirubin values below 0.12 mg per 100 ml. 107 patients with hepatocellular damage showed from 11—81 % after 5 minutes and from 19 to 100 % after 30 minutes. 33 cases of chronic hepatitis showed from 30 to 75 % after 5 minutes and from 33 to 100 % after 30 minutes. The authors conclude that a direct reaction above 50 % after 5 minutes or above 74 % after 30 minutes in a case with normal total serum bilirubin is pointing to liver damage; they are of the opinion that the direct reaction is of clinical value especially in cases with normal serum bilirubin concentration.

In studies on icterus neonatorum Waugh *et al.* (1940) found that the direct reaction showed a constant value of about 0.5 mg per 100 ml regardless of the intensity of the jaundice.

Writer's Observations.

The direct reaction was determined quantitatively in 10 normal men and 10 normal women (medical students and nurses) aged from 20 to 35 years (Table 1, Nos. 1—10 are men, Nos. 11—20

Table 1.

Normal Persons.

Obs. No.	Total bilirubin (mg per 100 ml)	Direct reaction (per cent of total bilirubin)		
		30 sec.	5 min.	30 min.
1	0.67	20	36	63
2	0.47	0	45	70
3	0.54	0	50	69
4	0.82	36	48	82
5	0.68	45	57	75
6	0.99	34	39	63
7	1.45	51	62	79
8	0.71	30	41	60
9	0.39	0	0	50
10	0.34	0	0	75
11	0.56	25	45	67
12	0.52	32	55	80
13	0.27	0	0	70
14	0.63	30	47	68
15	0.80	27	52	61
16	0.98	49	58	73
17	0.47	0	50	72
18	1.27	62	75	86
19	0.85	43	47	76
20	0.58	45	69	90

women). Reactions too weak to be read with any degree of accuracy (extinctions below 0.05) are given the sign »0».

In 10 normal newborn the direct reaction was determined with the same method in order to elucidate the direct reaction in icterus neonatorum; the samples were taken at the time when jaundice was most pronounced. Also some infants without visible jaundice were included in the investigation, the results of which are given in Table 2. Further the direct reaction after 30 seconds was determined in 50 normal newborn; 90 % of these showed values between 50 and 80 % of the total serum bilirubin and 10 % between 30 and 50 %; in a case of icterus gravis neonatorum the value 20 % was found. In 20 of the 50 cases daily determinations of the direct reaction (after 30 sec.) were carried out and only minor variations from day to day found (cf. Larsen & With, 1943).

Table 2.

Icterus neonatorum.

Obs. No.	Total bilirubin (mg per 100 ml)	Direct reaction (per cent of total bilirubin)		
		30 sec.	5 min.	30 min.
1	22.0	62	71	84
2	15.9	39	55	67
3	7.32	70	83	86
4	2.21	55	58	66
5	5.20	75	82	89
6	1.12	74	82	85
7	7.27	53	61	84
8	4.51	57	67	76
9	2.44	42	51	70
10	8.43	75	80	92

On 5 patients with hereditary hemolytic jaundice (Table 3, Nos. 1—3) and 2 with pernicious anemia (Table 3, Nos. 4—5) the direct reaction in jaundice of hemolytic origin was studied.

Table 3.

Jaundice of Hemolytic Origin.

Obs. No.	Total bilirubin (mg per 100 ml)	Direct reaction (per cent of total bilirubin)		
		30 sec.	5 min.	30 min.
1	3.16	21	29	43
2	2.15	19	28	45
3	2.72	32	35	54
4	2.57	22	32	37
5	2.71	17	36	52

In 7 patients with occlusive jaundice determinations were made (Table 4; Nos. 1—5, cholelithiasis; No. 6, neoplastic occlusion at papilla Vateri; No. 7, carcinoma of the gall-bladder with metastases to the liver).

Table 4.
Occlusive Jaundice.

Obs. No.	Total bilirubin (mg per 100 ml)	Direct reaction (per cent of total bilirubin)		
		30 sec.	5 min.	30 min.
1	4.86	42	53	79
2	8.18	53	67	72
3	1.80	51	56	68
4	7.68	72	83	86
5	2.35	43	67	78
6	11.3	58	76	86
7	52.0	69	77	91

In 15 patients suffering from catarrhal jaundice (Table 5) of varying severity determinations were made at the height of the jaundice; in one of the cases determinations were made during the fading of the jaundice too (obs. No. 1, a—d).

Table 5.
Acute Hepatitis.

Obs. No.	Total bilirubin (mg. per 100ml.).	Direct reaction (per cent of total bilirubin)		
		30 sec.	5 min.	30 min.
1 a	9.24	44	72	83
1 b	4.43	50	58	90
1 c	2.40	45	54	78
1 d	1.50	51	61	84
2	1.97	30	54	66
3	1.76	59	64	69
4	7.92	43	55	71
5	2.75	53	67	76
6	13.6	62	77	82
7	1.91	39	57	74
8	3.42	62	72	77
9	2.02	47	51	63
10	31.1	54	62	78
11	4.88	52	63	67
12	12.6	57	66	91
13	4.30	62	76	82
14	6.72	59	66	77
15	6.80	66	73	75

Table 6.

Chronic Hepatitis.

Obs. No.	Total bilirubin (mg per 100 ml)	Direct reaction (per cent of total bilirubin)		
		30 sec.	5 min.	30 min.
1	2.08	53	62	70
2	1.75	36	49	66
3	4.24	51	55	72
4	2.13	47	69	79
5	2.65	55	58	67
6	4.96	54	76	82

In Table 6 the results of the analysis in 6 cases of chronic hepatitis with slight jaundice are presented.

Discussion.

The variation within the single groups is seen to be considerable and the percentage found for the direct reaction shows marked overlapping from one group to the other; in spite of this overlapping, there is a distinct difference between some of the groups as seen

Table 7.

Mean Value and Extreme Values for the Direct Reaction.

Group	Direct reaction (per cent of total bilirubin concentration)								
	30 sec.			5 min.			30 min.		
	Minimum	Mean	Maximum	Minimum	Mean	Maximum	Minimum	Mean	Maximum
Normal persons[1]	(20)	(31)	62	(36)	(52)	75	54	71	90
Icterus neonat.	39	60	75	55	69	80	66	80	92
Hemolytic jaundice	17	23	32	28	32	36	37	46	54
Occlusive jaundice	41	55	72	53	70	77	72	75	91
Acute hepatitis	30	53	66	51	65	77	66	76	92
Chronic hepatitis	36	49	55	49	62	75	67	73	81

[1] The numbers in brackets indicate that in some of the cases the direct reactions were too weak for quantitative measurement (cf. Table 1) and the average is, therefore, calculated by the use of the rest of the values only.

from the survey given in Table 7 in which the mean values and the extreme values for the percentage of·the direct reaction in all the groups are seen (in the calculation for acute hepatitis only the value 1 a is reckoned for obs. No. 1).

Only the hemolytic jaundice and the occlusive jaundice show values so different that there is no overlapping. The values for icterus neonatorum are very similar to those of occlusive jaundice, a fact pointing against the hemolytic origin of this form of jaundice. Another fact pointing against the hemolytic origin of icterus neonatorum is the high values for the serum bilirubin often seen in this condition (often above 10 mg per 100 ml; cf. Larsen & With, 1943), as the serum bilirubin in hemolytic forms of jaundice most often shows values below 4 mg per 100 ml and practically always below 6 mg per 100 ml (With, 1943, c). So, our findings in icterus neonatarum show striking difference from those of Waugh *et al.* (cf. above), a divergence to which we have not been able to find any explanation.

The groups acute and chronic hepatitis show values much like the group occlusive jaundice and the normal persons show values about midway between hemolytic jaundice and occlusive jaundice. Our values show some divergence from the above-mentioned observations of Cantarow *et al.*, but this may readily be explained by the different analytical techniques used.

The diagnostic value of the quantitative direct reaction is, according. to Table 7, very limited; only in the differentiation of hemolytic jaundice from occlusive jaundice it may be of some value.

The readings of the direct reaction after 30 seconds, 5 and 30 minutes give practically parallel results in all the clinical groups. It thus seems unnecessary to perform more than one reading (*e.g.*, that after 5 minutes which is the most practical to carry out).

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Quantitative Studies on the Urinary Excretion of Bilirubin and Urobilinoids and on Serum Bilirubin in Diseases of the Liver and Jaundice without Liver Lesion.

By

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As pointed out previously by the author (With, 1942—43; 1, 2, 3, 4, 7) during the last couple of years the methods for quantitative determination of bilirubin in serum and urine and of the urobilinoids (urobilinogen, IX, α and stercobilinogen) in urine and feces have undergone considerable development; while earlier methods at disposal were to be regarded merely as semi-quantitative, the modern methods are reasonably accurate quantitative analytical procedures.

Hitherto, however, clinical reports of cases in which determinations with these modern methods have been made have not been published with the exception of Watson's (1937; 1940) which deal only with determination of urobilinoids. In the following simultaneous quantitative determinations of bilirubin and urobilinoids are to be presented.

Material and Methods.

For the sake of space case histories are omitted. The following groups were investigated: 1. hemolytic jaundice, 2. occlusive jaun-

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dice, 3. acute hepatitis, 4. chronic hepatitis. Further some determinations on normal persons are included. Yet another important group of jaundice, i. e., icterus neonatorum, has to be considered; studies on this condition were carried out with the same methods and published separately (Larsen & With, 1943).

As the methods have been discussed previously by the author, a detailed account may be omitted here. For serum bilirubin the method of Jendrassik & Gróf (1938) or With's micromodification (With, 1, 4, 7) was used; for urine bilirubin, the method of Jendrassik & Gróf (1938) was used (cf. With, 1942, 2), and for determination of urobilinoids the method of With (1942, 3).

Hemolytic Jaundice.

Three typical cases of hereditary hemolytic jaundice were investigated. The results are seen from Table 1.

Table 1.

Hemolytic Jaundice.

Case No. Date	1; woman aged 35 18/6 41; 19/4 43		2; woman aged 32 14/1 43	3; boy aged 10 28/1 43
Serum bilirubin (mg per 100 ml.)	2.72	2.08	3.16	2.61
Urine bilirubin	0	0	0	0
Urine uro- ⌠mg per 100 ml.	0.52	0.80	3.40	1.05
bilinoid ⌡mg per 24 hrs.	9.3	10.5	15.3	8.35

Occlusive Jaundice.

Eight cases were included in the study. The data are presented in *Table 2*. The cases of cholelithiasis and neoplastic occlusion were all typical ones. In Case 3 there were extensive liver metastases from a carcinoma of the gall-bladder and in Case 5 from a carcinoma of the coecum. The jaundice in such cases is to be regarded as due to intrahepatic biliary occlusion. In Case 7 «white bile» but nothing indicating neoplasma was found on operation (31. 1. 1943), but autopsy (24. 8. 1943) showed neoplasma papillae Vateri. Case 8 was a case of biliary xanthomatosis; it is somewhat

doubtful whether the jaundice in this case was of occlusive or parenchymatous origin; the case is published by Gerz (1, Case 1; 2, Case 4).

In Cases 4 and 6 passage of a gall-stone with consecutive rapid decrease of the serum bilirubin concentration and disappearence of the bilirubinuria was observed.

Acute Hepatitis.

31 cases were included in the study. The data of 27 of these are presented in *Table 3*, and the remaining in *Figures 1 to 4*. Several of the cases were neosalvarsan hepatitis, some were pregnant or puerperal women. Case 19 was a very grave one of long duration (jaundice over a month before the observation began). Case 31 was observed from the very beginning; the patient, whose wife fell ill with hepatitis a month before, was hospitalized for arterial hypertension; on Oct. 9th he observed a slight darkening of the urine and felt epigastric discomfort; on the following day, bilirubinuria (iodine test) and jaundice developed, and the feces were clay-colored on Oct. 11th. The other cases were typical »catarrhal jaundice» of varying duration and intensity (slight to medium degree of severity). Most of them came under observation within 10 days of the first appearance of the jaundice, while Cases 9, 11, 18, 19 and 20 came under observation 3—4 weeks and Case 16 2 months after the appearance of the jaundice. Some of the cases — about half — had dyspeptic complaints for one or two weeks before the jaundice appeared.

Chronic Hepatitis.

Seven cases were included in the study; the data are given in *Table 4*. Cases 1, 3, 5 and 6 showed hepatomegalia and more or less pronounced jaundice; consumption of greater amounts of alcohol does not seem to have taken place in any of these cases. Case 4 was a particularly severe case of half a year's duration; he died in hepatic coma one month after the observation.

Cases 2 and 7 were of particular interest as cases of unusually severe and protracted jaundice; they are to be described in some detail.

Case 2: Woman, aged 40. Previously no diseases of importance. In November 1941 she felt tired with epigastric discomfort. In January 1942 she developed jaundice. At this time there were several cases of epidemic hepatitis in her surroundings, and she and her son were admitted to the county hospital simultaneously. She stayed here for 6 weeks during which time jaundice subsided, but the liver was still palpable 2—3 cm below the costal margin at the discharge from the hospital; at this time the icterus index 6 was found. Two days after her departure from the hospital the jaundice recurred and persisted with varying intensity to her death, 11. 6. 1943. The color of the urine varied parallel to the jaundice and so did the color of the feces, which in periods were clay-colored. 21. 7. —8. 11. 1942 she stayed in Department A of the Rigshospital. The liver was at that time about 3 cm below the costal margin, and there were no signs of ascites or collateral circulation. The galactose test showed 3 g. excretion, the serum phosphatase was greatly increased, the serumprotein showed 2.4 % albumin and 5.6 % total protein, and the serum prothrombin was slightly decreased but becoming normal after 10 mg of vitamin K perorally. The serum citric acid was slightly increased — which in combination with the greatly elevated phosphatase commonly is assumed to suggest occlusive jaundice. There was no anemia and the platelet count was 290,000. 8. 11. 1942 she was readmitted to the county hospital; here the temperature, which had formerly been normal, became slightly elevated (ca. 38°), but intermittent fever suggestive of cholangitis never developed. The liver reached the umbilicus in the spring of 1943. The spleen was not palpable. She died at home with greatly enlarged abdomen, ascites and bloody diarrhoea.

As duodenal drainage, biopsy of the liver or autopsy were not performed one cannot exclude a slowly developing neoplastic occlusion similar to Case 7 of occlusive jaundice. The onset simultaneous with cases of epidemic hepatitis points, nevertheless, to an infectious origin, and the complete subsiding of the jaundice with persisting hepatomegalia also points to a chronic hepatitis and against a neoplastic biliary obstruction.

Case 7: Woman, aged 42. Previously no diseases of importance. In November 1941 she felt tired, and 3 weeks later she observed jaundice and dark urine. The jaundice has since persisted (*i.e.,* over 2 years) with varying intensity. Twice in the two years she has had gross hemorrhagic diathesis with consecutive anemia (to 20 % Hb) which each time responded excellently to transfusions and vitamin K. The feces have been completely clay-colored most of the time, but in periods more or less brown. The general condition has been good with the exception of tiredness. She has several times been admitted to a county hospital, and here laparotomy was performed (17. 9. 1942) to exclude biliary obstruction; the biliary passages were found to be normal, without dilatation, the liver great and intensively bile-colored but otherwise normal. She stayed in Department A, the Rigshospital 19. 9. 1943—19. 2. 1944. The liver was

Table 2.
Occlusive Jaundice.

Case No.; Diagnosis etc.	1; man, 69 years; neoplasma pancreatis				2; man, 68 years	
Date	22/8	19/11	20/11	25/11	11/12	12/12
Serum bilirubin mg per 100 ml	9.0	12.0	12.4	10.2	1.34	—
Urine bilirubin mg per 100 ml		12.1	10.5	11.5	0	0
Urine bilirubin mg per 24 hrs		132	105	128		
Urine urobilinoid mg per 100 ml		2.12	1.73	1.90	4.32	1.31
Urine urobilinoid mg per 24 hrs		23.3	17.3	22.0	47.5	18.1

Case No.	(2 continued) cholelithiasis			3; woman; 60 years; c. vesicae felleae				
Date	15/12	16/12	17/12	12/12	13/12	15/12	16/12	17/12
Serum bilirubin	1.01	—	1.43	32.0	42.0	39.4	36.5	40.8
Urine bilirubin per 100 ml	0	0	0	12.8	12.0	11.8	9.0	11.0
Urine bilirubin per 24 hrs				61.5	40.8	49.6	32.4	15.4
Urine urobilinoid per 100 ml	0.34	0.22	traces	0	0	0	0	0
Urine urobilinoid per 24 hrs	3.3	2.2						

Case No.	4; woman; 44 years; cholelithiasis				5; woman; 62 years; metastatic liver cancer		
Date	12/12	13/12	14/12	15/12	2/11	3/11	4/11
Serum bilirubin	7.68	11.1	Passage of gall-stone	1.70	9.20	—	1.87
Urine bilirubin per 100 ml	6.31	4.54		trace	1.40	2.32	—
Urine bilirubin per 24 hrs	—	—			12.3	17.4	18.7
Urine urobilinoid per 100 ml	0.	0		0	1.84	3.20	2.21
Urine urobilinoid per 24 hrs					16.2	24.0	22.1

Case No.	6; woman; 83 years; cholelithiasis					7; man; 37 years;			
Date	2/11	6/11	7/11	8/11	15/11	7/12	8/12	10/12	11/12
Serum bilirubin	8.54	9.32	Passage of	1.93	0.74	10.3	—	·	—
Urine bilirubin per 100 ml	4.04	4.26	gall-stone	0	0	5.80	2.24	2.22	1.92
per 24 hrs.	21.6	40.9				44.7	20.7	35.5	17.6
Urine urobilinoid per 100 ml	1.44	5.97		1.20	0.48	trace	trace	trace	0.91
per 24 hrs.	7.78	57.3		12.6	3.4				8.41

Case No.	(7 continued) neoplasma papillae Vateri; white bile, i.e. total occlusion.							
Date	13/12	14/12	15/12	16/12	17/12	18/12	20/12	21/12
Serum bilirubin	—	—	—	9.90	—	—	—	—
Urine bilirubin per 100 ml.	2.35	1.32	2.66	4.36	2.84	1.63	1.62	2.36
per 24 hrs.	16.0	7.58	20.5	42.3	51.8	17.4	14.6	21.6
Urine urobilinoid per 100 ml.	0.31	0.30	0.72	0.68	0.35	0.51	0.37	0.34
per 24 hrs.	2.12	1.95	5.40	6.57	6.47	5.41	3.31	3.16

Case No.	(7 continued)								
Date	28/12	20/12	2/1	6/1	12/1	18/1	27/1	28/1	30/1
Serum bilirubin	—	9.60	—	—	10.2	—	—	11.2	—
Urine bilirubin per 100 ml.	1.74	1.90	2.62	1.76	2.04	7.80	3.90	4.40	7.20
per 24 hrs.	13.1	17.3	28.9	19.7	17.7	31.2	39.0	35.2	43.2
Urine urobilinoid per 100 ml.	0.21	0	0	0	0	0	trace	trace	0
per 24 hrs.	1.59								

Case No.	8; man; 42 years; biliary xanthomatosis.		
Date	3/6	4/6	5/6
Serum bilirubin	—	26.1	19.2
Urine bilirubin per 100 ml.	6.62	6.81	5.31
per 24 hrs.	—	88.5	66.4
Urine urobilinoid per 100 ml.	0	0.23	0.25
per 24 hrs.		3.0	3.1

Table 3.

Acute Hepatitis.

Case No., Remarks	2; woman, 35 years; neosalvarsan jaundice; puerperium (delivery 7. 11.)						3; woman, 34 years				
Date	10/11	11/11	12/11	13/11	14/11	15/11	12/11	14/11	16/11	22/11	29/11
Serum bilirubin mg per 100 ml	—	9.74	16.6	15.6	11.8	5.8	9.40	3.11	0.81	1.01	0.73
Urine bilirubin { mg per 100 ml	1.86	5.50	5.80	5.30	5.10	6.20	2.10	0	0	0	0
mg per 24 hrs	9.9	66.0	116.0	53.0	45.9	72.1	12.6	0	0	0	0
Urine urobilinoid { mg per 100 ml	0						1.10	2.30	0.72	trace	0
mg per 24 hrs							6.60	25.3	10.8	trace	

Case No.	4; woman, 26 years; neosalvarsan jaundice; puerperium (delivery 22. 11.)									5; man, 57 years	
Date	23/11	24/11	25/11	26/11	27/11	28/11	29/11	1/12	3/12	3/12	4/12
Serum bilirubin	—	4.15	3.45	2.51	2.53	2.43	1.91	1.70	1.84	14.4	15.3
Urine bilirubin { per 100 ml	2.21	0.85	trace	0	0	0	0	0	0	5.42	3.91
per 24 hrs	18.0	9.3	trace	0	0	0	0	0	0	—	31.3
Urine urobilinoid { per 100 ml	1.62	5.30	2.10	trace	trace	0	0	0	0	3.24	4.02
per 24 hrs	13.0	61.0	26.4	trace	trace	0	0	0	0	—	32.2

Case No.	6; woman, 23 years											
Date	9/1	10/1	11/1	12/1	13/1	14/1	15/1	16/1	17/1	18/1	19/1	28/1
Serum bilirubin	5.78	5.04	—	3.58	1.01	0.93	1.03	0.80	—	0.80	1.46	0.99
Urine bilirubin { per 100 ml	0.35	—	0.60	0.25	0	0	0	0	trace	trace	0	0
per 24 hrs	—	—	2.50	0.95	0	0	0	0	trace	trace	0	0
Urine urobilinoid { per 100 ml	—	—	2.12	0.59	—	1.26	0.98	trace	trace	trace	0	0
per 24 hrs	—	—	8.90	2.30	—	13.5	10.5	trace	trace	trace	0	0

8; woman, 16 years

Date	5/1	6/1	7/1	8/1	9/1	10/1	12/1	14/1	16/1	19/1	24/1	3/2	13/2
Serum bilirubin	13.6	9.06	10.8	4.00	5.10	5.96	2.64	2.04	1.38	1.46	2.01	0.94	0.51
Urine bilirubin per 100 ml	7.36	5.72	4.20	1.72	trace	0	0	0	0	0	0	0	0
Urine bilirubin per 24 hrs.	—	23.2	44.3	18.0	trace	0	0	0	0	0	0	0	0
Urine urobilinoid per 100 ml	0	0	trace	0.52	0.55	3.68	1.74	0.68	0	0	0	0	0
Urine urobilinoid per 24 hrs.	0	0	trace	5.15	5.45	27.3	23.7	6.2	0	0	0	0	0

9; woman, 21 years; neosalvarsan jaundice (delivery 23.1.)

Date	23/1	24/1	26/1	28/1	19/1
Serum bilirubin	4.41	5.42	4.23	3.71	3.16
Urine bilirubin per 100 ml	trace	2.14	0.85	trace	0
Urine bilirubin per 24 hrs.	trace	45	10.2	trace	0
Urine urobilinoid per 100 ml	0	0	0	1.83	5.13
Urine urobilinoid per 24 hrs.	0	0	0	29	65

10; man, 20 years.

Date	17/2	18/2	19/2	20/2	21/2	22/2
Serum bilirubin	6.32	—	7.10	—	4.10	—
Urine bilirubin per 100 ml	1.51	4.40	2.81	0.62	0	0
Urine bilirubin per 24 hrs.	—	27.3	18.6	4.7	0	0
Urine urobilinoid per 100 ml	3.48	1.00	3.88	3.14	3.76	2.87
Urine urobilinoid per 24 hrs.	—	6.20	25.6	23.6	25.2	11.5

(10 continued)

Date	23/2	25/2	27/2	3/3	5/3	11/3	16/3
Serum bilirubin	4.34	—	3.40	2.42	1.17	0.81	0.41
Urine bilirubin per 100 ml	0	0	0	0	0	0	0
Urine bilirubin per 24 hrs.	0	0	0	0	0	0	0
Urine urobilinoid per 100 ml	0.89	0.17	trace	0	0	0	0
Urine urobilinoid per 24 hrs.	5.50	0.51	trace	0	0	0	0

12; woman, 35 years.

Date	26/3	27/3	30/3	31/3	1/4	8/4
Serum bilirubin	9.92	7.86	—	2.13	—	0.69
Urine bilirubin per 100 ml	4.64	trace	0	0	0	0
Urine bilirubin per 24 hrs.	65.6	trace	0	0	0	0
Urine urobilinoid per 100 ml	0.46	trace	trace	0	0	0
Urine urobilinoid per 24 hrs.	6.4	trace	trace	0	0	0

Table 3, continued.

Case No.	13; man, 69 years; previously heavy consumption of alcohol								11; woman, 16 years				
Date	28/3	30/3	3/4	8/4	12/4	17/4	22/4	29/4	6/5	15/5	22/5	27/5	15/6
Serum bilirubin	7.12	3.81	3.51	3.03	2.90	2.72	2.12	1.91	3.42	2.07	1.46	1.21	0.82
Urine bilirubin { per 100 ml	2.46	trace	0	0	0	0	0	0	0	0	0	—	0
{ per 24 hrs.	24.6	trace	0	0	0	0	0	0	0	0	0	—	0
Urine urobilinoid { per 100 ml ..	1.23	0.71	0.82	0.65	0.49	0.32	0.37	0	1.72	trace	trace	0	0
{ per 24 hrs..	12.3	9.5	8.6	12.4	10.3	5.42	4.45	0	19.8	trace	trace	0	0

Case No.	15; man, 21 years;		16; man, 53 years; subchronic case						17; woman, 17 years; neo-			
Date	7/5	8/5	16/6	17/6	18/6	24/6	4/7	31/8	12/9	15/9	17/9	20/9
Serum bilirubin	7.61	5.92	2.57	2.32	2.93	1.94	2.02	0.88	3.57	5.32	4.89	4.02
Urine bilirubin { per 100 ml	0	0	0	0	0	0	0	0	2.03	2.19	0	0
{ per 24 hrs.	0	0	0	0	0	0	0	0	—	24.1	0	0
Urine urobilinoid { per 100 ml ..	0.38	0.53	—	0.63	0.46	1.36	0	0	0.63	0.78	1.24	0.94
{ per 24 hrs..	3.99	6.90	—	10.1	8.7	13.3	0	0	—	8.6	9.3	4.0

Case No.	salvarsan jaundice					18; woman, 18 years; neosalvarsan jaundice in pregnancy (7. month).						
Date	23/9	1/10	5/10	8/10	27/10	12/10	14/10	16/10	20/10	21/10	28/10	2/1
Serum bilirubin .... "	—	1.94	—	2.03	0.58	3.68	—	—	4.88	—	—	0.79
Urine bilirubin { per 100 ml	0	0	0	0	0	0	0	0	0	0	0	0
{ per 24 hrs.	0	0	0	0	0	0	0	0	0	0	0	0
Urine urobilinoid { per 100 ml ..	0.62	0.43	0.81	0.62	0	1.69	0.27	0.73	0.21	0.46	0.19	0
{ per 24 hrs..	5.9	8.0	13.9	7.5	0	15.2	2.25	4.35	5.50	5.04	2.01	0

Case No. 20; man, 56 years

	26/10	28/10	30/10	1/11	9/11
Serum bilirubin	—	4.30	—	1.79	0.61
Urine bilirubin per 100 ml	0	0	0	0	0
Urine bilirubin per 24 hrs	0	0	0	0	0
Urine urobilinoid per 100 ml	0.37	trace	0.25	trace	0
Urine urobilinoid per 24 hrs	3.37	trace	2.46	trace	0

Case No. 21; man, 27 years

	2/11	4/11	7/11	12/11
Serum bilirubin	6.72	—	5.82	2.86
Urine bilirubin per 100 ml	1.82	1.50	trace	0
Urine bilirubin per 24 hrs	—	22.3	trace	0
Urine urobilinoid per 100 ml	trace	0.61	1.86	0
Urine urobilinoid per 24 hrs	trace	8.80	22.3	0

Case No. 22; man, 22 years

	22/11	24/11	26/11
Serum bilirubin	6.71	7.96	—
Urine bilirubin per 100 ml	3.05	0.88	1.48
Urine bilirubin per 24 hrs	15.1	13.1	20.1
Urine urobilinoid per 100 ml	0	0	0
Urine urobilinoid per 24 hrs	0	0	0

Case No. 25; woman

	17/11	19/11
Serum bilirubin	1.97	—
Urine bilirubin per 100 ml	0	0
Urine bilirubin per 24 hrs	0	0
Urine urobilinoid per 100 ml	0.26	0.18
Urine urobilinoid per 24 hrs	1.70	1.08

Case No. (22 continued)

	28/11	30/11	3/12
Serum bilirubin	3.20	—	1.72
Urine bilirubin per 100 ml	trace	0	0
Urine bilirubin per 24 hrs	trace	0	0
Urine urobilinoid per 100 ml	1.90	0.23	0.10
Urine urobilinoid per 24 hrs	38.0	4.52	1.67

Case No. 23; man, 42 years

	16/12	18/12	19/12
Serum bilirubin	23.0	—	29.6
Urine bilirubin per 100 ml	4.21	5.50	—
Urine bilirubin per 24 hrs	71.5	59.1	—
Urine urobilinoid per 100 ml	1.86	0.93	—
Urine urobilinoid per 24 hrs	31.6	21.3	—

Case No. 24; man, 28 years

	28/10	30/10	3/11	9/11
Serum bilirubin	3.42	—	1.87	1.46
Urine bilirubin per 100 ml	0	0	0	0
Urine bilirubin per 24 hrs	0	0	0	0
Urine urobilinoid per 100 ml	3.48	0.21	trace	0
Urine urobilinoid per 24 hrs	36.5	2.06	trace	0

Case No. — ; 16 years

	21/11	24/11
Serum bilirubin	—	0.48
Urine bilirubin per 100 ml	0	0
Urine bilirubin per 24 hrs	0	0
Urine urobilinoid per 100 ml	trace	0
Urine urobilinoid per 24 hrs	trace	0

Case No. 26; man, 18 years

	25/11	26/11	29/11	2/12	3/12	13/12
Serum bilirubin	—	3.41	—	—	2.00	0.83
Urine bilirubin per 100 ml	0	0	0	0	0	0
Urine bilirubin per 24 hrs	0	0	0	0	0	0
Urine urobilinoid per 100 ml	1.55	2.10	0.60	0.92	trace	0
Urine urobilinoid per 24 hrs	33.5	50.4	6.6	10.2	trace	0

Case No. 27; woman, 31 years; pregnancy (6' month)

	20/12	28/12	30/12	5/1
Serum bilirubin	1.67	—	—	0.78
Urine bilirubin per 100 ml	0	0	0	0
Urine bilirubin per 24 hrs	0	0	0	0
Urine urobilinoid per 100 ml	1.50	0.11	trace	0
Urine urobilinoid per 24 hrs	27.8	0.72	trace	0

Table 3, continued.

28; woman, 36 years

Case No.							
Date	18/1	20/1	22/1	26/1	30/1	9/2	19/2
Serum bilirubin	6.80	—	—	2.67	—	1.02	0.63
Urine bilirubin { per 100 ml	1.96	0.78	trace	0	0	0	0
{ per 24 hrs.	4.90	1.95	trace	0	0	0	0
Urine urobilinoid { per 100 ml	2.60	6.76	8.32	1.15	0.56	0.22	0.12
{ per 24 hrs.	6.33	16.9	41.6	13.8	4.44	2.23	1.14

29; woman, 29 years; untreated syphilis latens; chr. otitis

Case No.							
Date	15/1	19/1	21/1	23/1	27/1	2/2	9/2
Serum bilirubin	—	12.6	—	3.92	3.23	—	1.42
Urine bilirubin { per 100 ml	2.88	0.86	0.72	0	0	0	0
{ per 24 hrs.	18.7	6.05	5.40	0	0	0	0
Urine urobilinoid { per 100 ml	0.20	0.29	1.74	0.31	0.26	0.18	0.10
{ per 24 hrs.	1.30	2.03	13.1	3.40	1.91	1.00	0.78

31; man, 45 years

Case No.		
Date	11/10	12/10
Serum bilirubin	5.60	—
Urine bilirubin { per 100 ml	1.62	0.78
{ per 24 hrs.	9.72	8.46
Urine urobilinoid { per 100 ml	0.24	trace
{ per 24 hrs.	1.44	trace

30; woman, 38 years; mapharsene jaundice

Case No.											
Date	9/2	12/2	14/2	16/2	18/2	20/2	22/2	28/2	2/3	8/3	15/3
Serum bilirubin	17.3	—	9.24	—	—	—	4.43	—	2.40	1.90	1.50
Urine bilirubin { per 100 ml	10.0	3.40	1.10	0.74	trace	0	0	0	0	0	0
{ per 24 hrs.	40.0	29.7	15.9	8.12	trace	0	0	0	0	0	0
Urine urobilinoid { per 100 ml	0	0	0	trace	2.81	0.98	1.43	0.21	0.17	0.11	0
{ per 24 hrs.	0	0	0	trace	36.5	11.3	14.1	2.0	1.82	1.37	0

(31 continued)

Case No.						
Date	13/10	14/10	15/10	18/10	20/10	22/10
Serum bilirubin	—	—	—	—	1.50	—
Urine bilirubin { per 100 ml	1.00	1.40	0.52	0	0	0
{ per 24 hrs.	8.00	14.7	7.54	0	0	0
Urine urobilinoid { per 100 ml	trace	0.14	0.63	0.19	0.21	0
{ per 24 hrs.	trace	1.48	9.14	1.40	3.36	0

at that time palpable 3—4 cm below the costal margin, there was no splenomegalia, no ascites and no sign of collateral circulation. Duodenal drainage was performed 3 times, and each time the stimulation with magnesium sulphate was followed by a flow of light yellow bile (from 25 to 80 ml). Liver biopsy showed well-preserved liver cells without deposits of lipoids, only slight accumulation of bile pigment in the tissue, some proliferation of connective tissue in the porto-biliary spaces with slight infiltration with lymphocytes and histiocytes, no proliferation of the fine bile ducts, no signs of specific inflammation or neoplasma. Histologic diagnosis: Chronic hepatitis.

She showed — like Case 2 — greatly elevated serum phosphatase and slightly increased serum citric acid; serum cholesterol about 400 mg per 100 ml. The serum prothrombin was determined serveral times; it became dangerously low when regular administration of vitamin K was omitted. When 2 mg of vitamin K (Kvitasol »Leo») was given once a week, the prothrombin could be maintained between 30 and 100 % of the normal. The Bauer galactose test was normal (0.3 g). The serumprotein was 7.5 %. There was no anemia or thrombopenia. The serum iron was considerably increased (226 γ per 100 ml; Brochner-Mortensen & Olsen's method).

Case 7 thus shows great similarity to Case 2, but the course was even more protracted here. The diagnosis chronic hepatitis seems to be adequately established although the behaviour of the serum prothrombin (vitamin K sensivity; Hansen & Begtrup, 1943), the serumphosphatase and the serum citric acid suggest occlusive jaundice.

In both Case 2 and 7 the urine once, when the jaundice was at its highest, showed »black diazo reaction» (cf. Table 3). This reaction was, however, found only in the urine on a single day. This phenomenon, also observed by Jendrassik & Gróf (1938) in the urine from long standing cases of jaundice, is somewhat obscure.

Observations on Normal Persons.

The normal values of the serum bilirubin have been investigated previously by the author (With, 1943, 7). The excretion per 24 hours with the feces and the urine was determined on 20 patients with regular stool without injury to the liver or bile passages, blood diseases or febrile infections. The fecal excretion was determined in 4 × 24 hour periods and the average value for the 24-hour excretion calculated (cf. Watson, 1937). The feces analyses were carried out with the method of With, and 10 g were taken for the analysis and brought into a volume of 160 ml before the addition of ferrous hydroxide. The results are presented in *Table 5*.

Table 4.

Chronic Hepatitis.

Case No. Remarks etc.	1; woman, 40 years	2; woman, 40 years; see the text					
Date	21/11	12/10	14/10	16/10	18/10	20/10	22/10
Serum bilirubin mg per 100 ml	6.12	9.16	—	—	—	11.8	—
Urine bilirubin { mg per 100 ml	0.85	2.72	3.36	3.62	4.34	5.12	3.60
mg. per 24 hrs.	10.2	29.9	47.6	51.5	56.5	35.8	43.2
Urine urobilinoid { mg per 100 ml	2.13	0.41	0.20	0.25	0.20	0.47	0.16
mg. per 24 hrs.	25.6	4.51	2.79	3.61	2.76	3.29	1.97

Case No.	(2 continued)							3; woman, 19 years	
Date	24/10	26/10	28/10	30/10	2/11	4/11	6/11	25/11	27/11
Serum bilirubin	—	8.53	—	—	13.6	—	—	2.14	—
Urine bilirubin { per 100 ml	2.62	3.50	black diazo	6.30	4.00	6.90	4.80	0	0
per 24 hrs.	28.8	35.0	reaction	48.3	19.2	38.0	62.4	0	0
Urine urobilinoid { per 100 ml	0.16	0.16	0	0	0.46	0.13	trace	0.11	0.41
per 24 hrs.	1.74	1.60	0	0	2.20	0.70	trace	0.41	3.24

Case 4; man, 34 years; liver cirrhosis

Date	29/11	10/12	29/4	8/5	18/5
Serum bilirubin	—	1.67	3.58	4.41	8.95
Urine bilirubin — per 100 ml	0	0	trace	0	0
Urine bilirubin — per 24 hrs.	0	0	trace	0	0
Urine urobilinoid — per 100 ml	2.22	1.21	16.3	2.15	7.18
Urine urobilinoid — per 24 hrs.	4.44	7.26	130	36.5	96.2

Case 5; man, 62 years

Date	4/1	6/1	8/1	10/1	12/1	14/1
Serum bilirubin	4.96	—	—	—	3.60	—
Urine bilirubin — per 100 ml	trace	0	0	0	0	0
Urine bilirubin — per 24 hrs.	trace	0	0	0	0	0
Urine urobilinoid — per 100 ml	1.29	2.72	1.03	0.82	5.36	1.74
Urine urobilinoid — per 24 hrs.	10.3	24.5	4.36	8.20	48.2	15.2

Case 5 (continued)

Date	20/1	24/1	28/1	1/2	7/2	15/2	23/2	2/3
Serum bilirubin	—	—	2.98	—	2.63	1.97	1.75	0.32
Urine bilirubin — per 100 ml	0	0	0	0	0	0	0	0
Urine bilirubin — per 24 hrs.	0	0	0	0	0	0	0	0
Urine urobilinoid — per 100 ml	1.30	1.38	0.72	0.37	0.49	0.41	0.30	0
Urine urobilinoid — per 24 hrs.	8.85	6.21	5.00	3.14	3.66	4.51	3.91	0

Case 6; woman, 41 years

Date	20/1.	22/1.
Serum bilirubin	2.16	—
Urine bilirubin — per 100 ml	0	0
Urine bilirubin — per 24 hrs.	0	0
Urine urobilinoid — per 100 ml	2.65	1.69
Urine urobilinoid — per 24 hrs.	7.95	10.2

Case 7; woman, 42 years; see the text

Date	21/9	23/9	27/9	4/10	10/10	13/10	15/10	17/10
Serum bilirubin	10.3	13.8	10.8	9.2	—	6.0	—	7.2
Urine bilirubin — per 100 ml	—	—	black diazo reaction	—	0.84	1.10	1.56	1.56
Urine bilirubin — per 24 hrs.	—	—		—	9.24	14.3	21.2	20.3
Urine urobilinoid — per 24 hrs.	—	—	—	—	0.63	0.41	0.51	trace
Urine urobilinoid — per 100 ml	—	—	—	—	6.97	5.36	7.41	trace

Table 5.

Urinary and Fecal Urobilinoid in »Normal» Persons.

Sex	Age	Diagnosis	Feces	Urine	Quotient
M	54	Bronchial asthma	25.1	0.40	1.6
F	30	Bronchial asthma	35.2	Trace	< 1
M	36	Bronchial asthma	62.9	0.26	< 1
M	48	Chronic gastritis	41.2	Trace	< 1 .
F	32	Rheumatic fever (afebrile stage)	71.0	1.70	2.4
F	28	Chronic polyarthritis ..	40.7	0.25	< 1
F	62	Diabetes mellitus (slight case)	59.6	0.45	< 1
F	40	Chronic polyarthritis ..	87.1	. 1.08	1.2
F	28	Rheumatic fever (afebrile stage)	70.2	Trace	< 1
M	33	Bronchial asthma	164	1.41	< 1
F	23	Puerperal albuminuria ..	68.2	2.01	3.0
F	46	Chronic polyarthritis ..	83.2	2.24	2.7
M	24	Chronic gastritis	224	0.95	< 1
M	36	Sciatica	152	1.03	< 1
M	35	Mitral stenosis	87.8	1.12	1.2
F	23	Myalgia	73.5	2.58	3.5
F	45	Neurasthenia	110	1.25	1.2
M	26	Cardiac neurosis	124	0.57	< 1
M	36	Peptic ulcer	37.0	0	0
F	35	Neurasthenia	44.2	Trace	< 1

The urobilinoid excretions are given in mg per 24 hours and the »Quotient» (urobilin quotient) is the urinary excretion expressed in percentage of the fecal excretion (Adler & Sachs, 1923).

Discussion.

For practical reasons the serum bilirubin, the urinary excretion of bilirubin, the urinary excretion of urobilinoids and the fecal excretion of urobilinoids are to be discussed separately. A more detailed discussion of the urinary excretion of bilirubin is, however, not included as the author recently has published a paper on this subject (With, 1943, 5).

The Serum Bilirubin Concentration as an Expression of the Liver Function or the Degree of Biliary Occlusion.

The clinical significance of the serum bilirubin concentration is illustrated by *Diagram 1* which gives the maximal values of such of our cases which were subjected to investigation at the time of their maximal degree of jaundice. The average value for the maximal attained serum bilirubin concentration was 18.6 mg per 100 ml for occlusive jaundice, 8.8 for acute hepatitis. This is due to the reatively great amount of slight cases of hepatitis but also to some cases of complete biliary obstruction with intense jaundice; presumably also a certain number of less severe cases of obstructive jaundice exists, but such cases are as a rule not admitted to hospital and therefore not included in the material. As the values in the two groups show considerable overlapping one cannot use the maximal attained height of the serum bilirubin in the differential diagnosis between occlusive jaundice and hepatitis.

Of great interest is Case 7 of occlusive jaundice in which complete obstruction (»white bile»; cf. Gade, 1943) was found at operation and which showed, nevertheless, as low a serum bilirubin as ca. 10 mg per 100 ml — a value maintained for more than a month. That the biliary obstruction was complete a considerable length of time before the operation is indicated by the fecal analysis, which 7.—11. 12 showed a daily urobilinoid excretion of only 1.4 mg per 24 hours.

This low serum bilirubin in a case of proved complete obstruction cannot be due to a particularly great urinary excretion of bilirubin as the average excretion was only ca. 25 mg per 24 hours. If this is compared with, *e.g.*, Case 19 of acute hepatitis it is seen that this case shows a considerably greater bilirubin excretion with the urine (average ca. 75.2 mg per 24 hours) and a much higher serum bilirubin (ca. 30 mg per 100 ml); and further, this patient with hepatitis excreted bilirubin into the intestine giving rise to an urobilinuria of about 75 mg per 24 hours while our case of occlusive jaundice did not excrete any bilirubin into the intestine. The low serum bilirubin in our case must be considered due to low production of bilirubin and not to high excretion through the kidneys.

This leads to the interesting question about the *individual variation in the bilirubin production* which is to be treated more detailed in another paper (With, 1944, 11). It is important to know that such a variation takes place, as it means that the *serum bili-*

Diagram 1.

The serum bilirubin in

occlusive jaundice and hepatitis

(Maximal values).
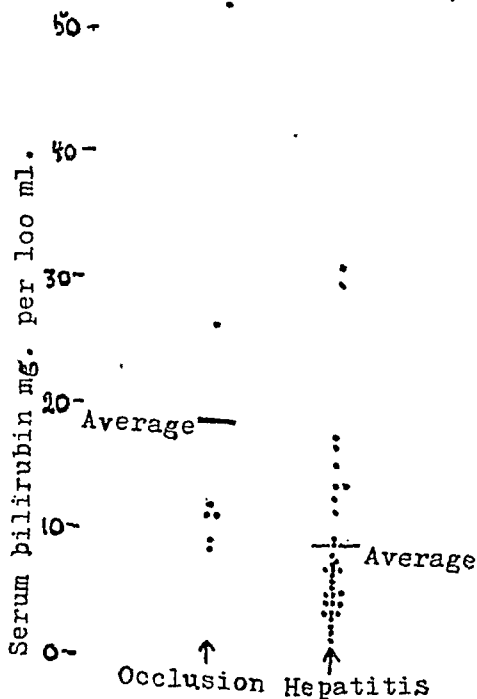
rubin concentration is not only an expression of the degree of occlusion — or in hepatitis the degree of injury to the parenchyma — but is also *to a great extent influenced by the bilirubin production level of the patient in question,* a factor which in most cases is unknown. As the bilirubin production level may show considerable variation it is easily understood that this factor is not without interest.

The variation of the serum bilirubin concentration in cases showing total biliary obstruction was also noted by Watson (1937, 1940) who most often found the icterus index above 100, but not uncommonly between 50 and 100 and seldom between 20 and 50 in such cases (icterus index = ca. 5 times the serum bilirubin concentration in mg. per 100 ml). Watson was, however, not able to exclude the possibility that this variation might be due to greater urinary excretion of bilirubin in the cases with low *serum* bilirubin concentration. That this explanation is very improbable is shown by recent observations on the relation between serum bilirubin and urinary bilirubin (With, 1943, 5) showing that high values of urinary bilirubin

correspond to high values of serum bilirubin. But simultaneous determinations of the urinary excretion of bilirubin and the serum bilirubin in cases of total biliary obstruction have not been carried out before (cf. Watson, 1940, p. 2431).

Velocity of Variations of the Serum Bilirubin.

The form of variation observed in our cases is only the fluctuation of the serum bilirubin at the height of the jaundice and the decrease of the serum bilirubin parallel to the subsiding of a hepatitis or the removal of a biliary obstruction (cf. Fig. 1—4). The rise of the serum bilirubin in the beginning of a hepatitis or an obstructive process is practically impossible to observe clinically as the patients are first seen after jaundice has set in. So, our knowledge of the rising serum bilirubin is mainly based on experimental data, but our Case 31 of acute hepatitis which developed during the stay at the hospital shows that a jaundice of 5.60 mg per 100 ml may develop within 24 hours. That an abrupt initial rise in the serum bilirubin may take place is also likely in view of the variations at the height of the disease (cf. Fig. 2).

Fig.1.

Acute hepatitis,Case 1.

Fig.2.
Acute hepatitis, Case 7.
Serum bilirubin——
Urine bilirubin·····
Urine urobilinoid———
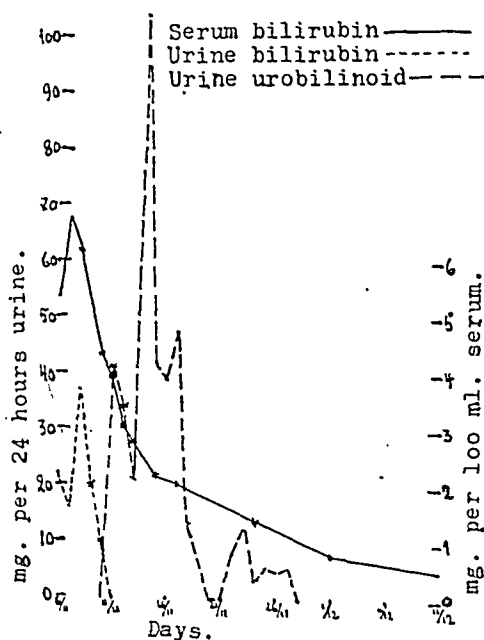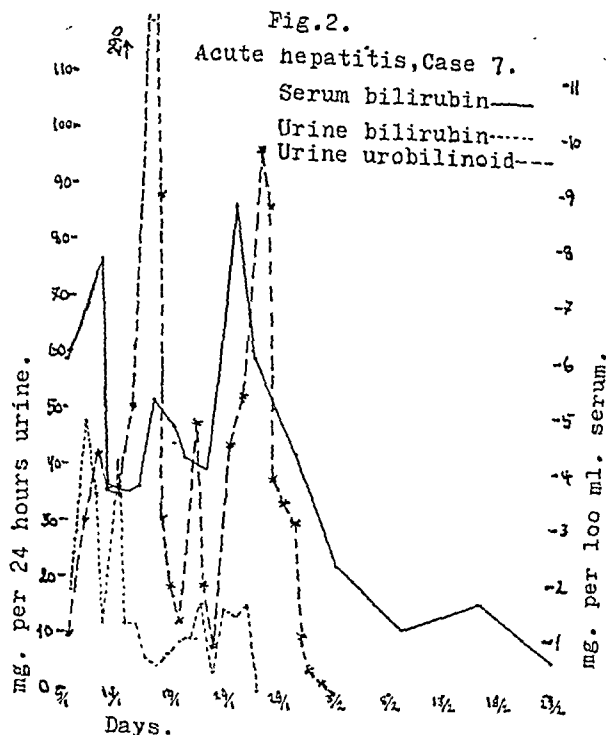
The decrease of the jaundice in hepatitis is on the contrary a slow process. On the other hand, the decrease of a jaundice due to obstruction takes place very rapidly as seen from Cases 4 and 6, in which the serum bilirubin fell from 11.1 to 1.70 and from 9.32 to 1.93 in the course of the day of the passage of the gall-stone. As the serum bilirubin in these cases had not reached normal values on the morning after the passage of the stone, one has to assume that it takes some time and probably more than 24 hours before the normal serum bilirubin level is reached after the removal of a biliary obstruction. Still, the fall of the serum bilirubin is unquestionably very rapid under these circumstances, but our material does not elucidate this process in detail.

The Duration of Hyperbilirubinemia in Acute Hepatitis.

The duration of the hyperbilirubinemia in acute hepatitis is of special clinical interest, as the serum bilirubin often remains slightly increased after all the commonly used functional liver

Table 6.

Duration of Hyperbilirubinemia and Urobilinuria in Acute Hepatitis.

Case	No.	1	3	4	6	7	8	10	11	12	13	17	19	21	22	28	29	30
S. B.	≧ 2	≧ 6	> 2	≧ 3	0	~ 8	5	11	~23	~1	~21	~23	·13	>4	~30	~2		
S. B.	≧ 1	≧13	≧10	7	3	~21	21	13	~23	~1	~26	~22	~16	>4	~26	~13	~15	~2
U. U.	≧ 3	~16	3	0	3	3	3	3	6	0	~19	~23	14	0,3	~~16			

S.B. ≧ 2: Number of days until the serum bilirubin concentration decreased to below 2 mg per 100 ml.

S.B. ≧ 1: Number of days until the serum bilirubin concentration decreased to below 1 mg. per 100 ml.

U. U. ≧ 3: Number of days until the urinary urobilinoid (mg. per 24 hours) decreased to below 3.

The number of days is reckoned from the first day on which the urine was bilirubin-free.

tests have become normal. In *Table 6* a comparison of the urobilinuria and the hyperbilirubinemia in acute hepatitis is given; only the cases which showed bilirubinuria are included in the table, and the duration is given in days reckoned from the first day bilirubin was absent from the urine.

Table 6 shows that *in most cases of acute hepatitis the serum bilirubin is increased after the urinary excretion of urobilinoids has reached normal values.* As the limit used for the urinary urobilinoid (3 mg per 24 hrs) is only seldom reached by normal persons, it is more correct to compare with the upper limit (2 mg per 100 ml) for the serum bilirubin than with the lower one; this upper limit for the serum bilirubin is also only reached by a few normal subjects (With, 1943, 7). But even by comparison with the upper normal limit for the serum bilirubin the greater part of the cases shows a longer duration of the hyperbilirubinemia than of the urobilinuria. On the other hand, a certain number of cases show a longer duration of the urobilinuria and in several cases the observations do not give conclusive evidence of which of the two pathological phenomena shows the longer duration.

As urobilinuria is commonly assumed to be the most sensitive expression for damage of the liver parenchyma (cf. Eppinger, 1937, p. 280) it is of interest to know that this rule does not hold good in cases of acute hepatitis, as in most of these the increase in serum

bilirubin is a more sensitive expression than the urobilinuria. This has already been pointed out by Meulengracht (1919) who only mentioned the fact without giving more detailed documentation. This observation of Meulengracht seems, however, not to have attracted sufficient attention and has not been commonly known. Perhaps the urobilinuria is the test of choice in chronic hepatitis; our material does not give conclusive evidence on this point (cf. below).

As an explanation of the long duration of the bilirubinemia in acute hepatitis one might think of the derangement of the parenchyma with consecutive destruction of the bile capillaries which is found in all cases — even the slight — of acute hepatitis (cf. Roholm, Krarup & Iversen, 1942). This destruction of the bile capillaries causes a secretion into the lymph spaces and a »lymphogenous jaundice« (cf. With, 1944, 9). Only at the time when all the bile capillaries are reformed can this lymphogenous jaundice be expected to subside, and the rebuilding of the bile capillaries may very well take a longer time than the restoration of the functions of the parenchyma.

Bilirubinuria in Occlusive Jaundice and Hepatitis.

In a previous paper (With, 1943, 5) the author has reported his investigation on the threshold value for the serum bilirubin which marks the appearance of bilirubinuria, the relation between the bilirubin concentration in serum and urine, the dependence of bilirubin excretion on the kidney function and the rôle of the so-called direct-reacting bilirubin of the serum in the urinary excretion of bilirubin. Consequently, a discussion of these interesting problems can be omitted here, and we shall only deal with the absolute value of the urinary bilirubin excretion and its clinical significance. Some problems concerning bilirubinemia are discussed below in the section on the transition of bilirubinuria into urobilinuria in acute hepatitis.

In Diagram 2 the maximum values for the excretion of bilirubin and urobilinoid in the investigated cases are given as concentrations in 24-hour urine and mg excreted per 24 hours. Only cases with bilirubinuria are, of course, included in the bilirubin section of the diagram, for which reason there are more points in the urobilin section than in the bilirubin section. The average maximum bilirubin excretion in occlusive jaundice (7.2 mg per 100 ml, 64.4 mg per 24 hours) is greater than in hepatitis (4.8 and 43.2), but

Diagram 2.
Urine bilirubin and urobilinoid.
(Maximal values).

Bilirubin x
Urobilinoid ·
Average values——
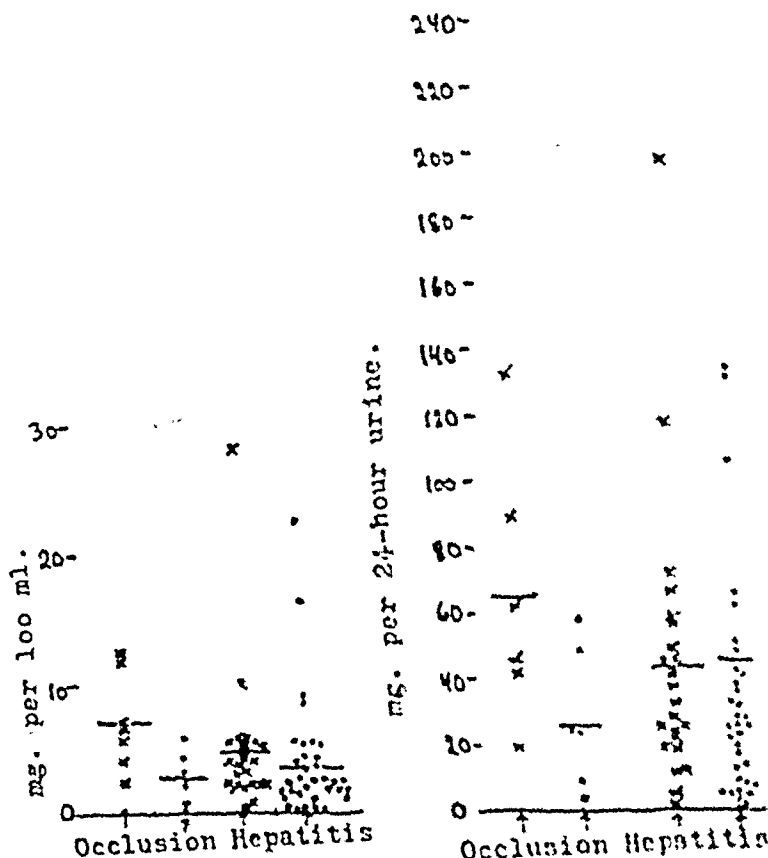
the difference is only small. For the urobilinoid excretion the opposite is the case, as the average for hepatitis (3.5 and 45.6) here is greater than for occlusive jaundice (2.8 and 25.6).

Urobilinuria in Normal Persons and in Hemolytic Jaundice; General Remarks on Urobilinuria.

The urinary urobilinoid excretion in normal persons is illustrated in Table 5. Values up to 2.58 mg per 24 hours are found

but only 3 persons showed above 2 mg and 25 per cent of the persons showed trace or no excretion. Watson (1937) came — with a very similar method of analysis — to values in close agreement with ours.

The three cases of hemolytic jaundice showed values from 8 to 15.3 mg per 24 hours, *i.e.*, a moderately but definitely augmented excretion. Also Watson (1937) found a slightly increased excretion in most of the 13 cases investigated by him, and in some a greatly increased excretion. But the latter was found only in cases complicated by acute hemolytic crisis, splenic infarction or during anesthesia. The nature of the urobilinuria in hemolytic jaundice has been subject to discussion; some authors hold that it is merely a sequel to the greatly augmented production of urobilinoids in this condition, while others hold that this explanation is insufficient and it is necessary to assume a certain degree of damage to the liver as well (Watson, 1937).

Watson thinks that the capacity of the liver for excretion of urobilinoids is utilized to the very limit under normal circumstances in these cases and that, consequently, the least damage to the liver (general infections, anesthesia etc.) gives rise to considerably greater urobilinuria than is the case in normal persons. He arrived at this conclusion because the fecal urobilinoid showed about the same value in his cases with great urobilinuria and in those with moderate urobilinuria, a finding which compelled him to seek the cause of the variation in the urinary excretion in differences in the liver function.

This trend of reasoning is also of value in the case of normal individuals, as we have seen that the bilirubin production — and herewith the production of urobilinoids — shows a considerable individual variation. It may seem likely that one individual producing much more urobilinoid than another develops urobilinuria with minor damage to the liver than does this other one. Accordingly, we have to take into account that the urinary excretion of urobilinoids is not exclusively a result of the degree of damage to the liver but is also dependent on the level of bilirubin production. A simple line of reasoning is, however, sufficient to show that the *urobilinuria in diseases of the liver must be grossly independent of the bilirubin production level.*

One imagines two cases of liver disease with the same degree of damage to the liver but with the difference that Case A has a bilirubin production level which is 2 times as great as that of Case B. As both livers are capable of the same bilirubin excretion, the serum bilirubin concentration in Case A will be more than two times that of Case B as the diseased liver cannot excrete all the bilirubin produced by B and *therefore none* of the extra amount produced by A. Provided that the kidney function

Fig. 3.

Acute hepatitis, Case 11.
Serum bilirubin
Urine bilirubin
Urine urobilinoid
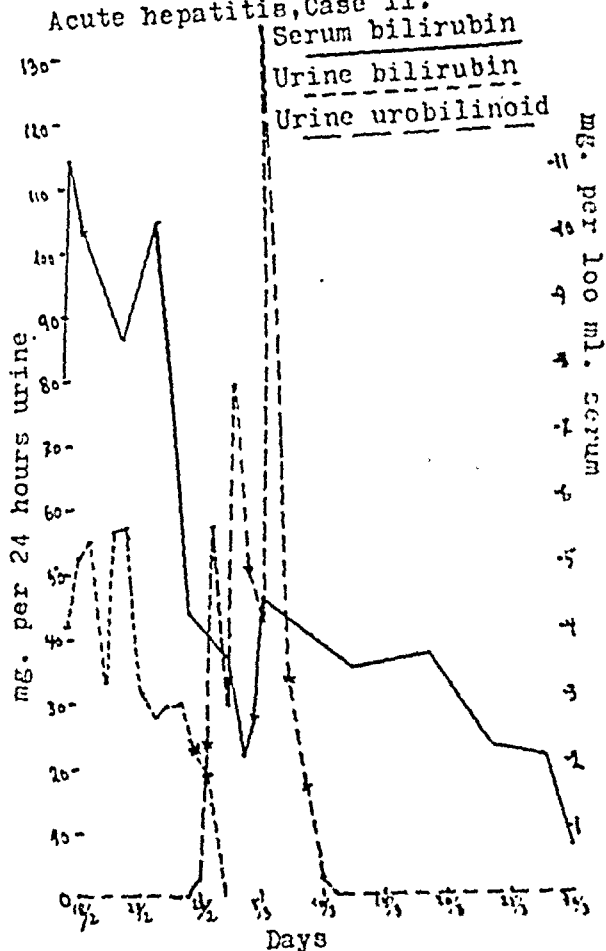
is the same in A and B the bilirubinuria will be considerably greater in A than in B. On the other hand, the urobilinoid formation in the intestine is the same in both cases, as the bilirubin excretion with the bile is the same — provided the intestinal flora and other conditions in the intestines are identical. And as the liver and kidney function were identical in the two cases the urobilinuria is, consequently, also identical in A and B.

On the other hand, it is readily seen that the bilirubin production level sets certain limits for the urobilinuria; if for example the production level is 50 mg per 24 hours it is of course impossible to find a urobilinuria greater than 50 mg per 24 hours even in the case of severe liver damage. So, *the upper limit of the urobilinuria due to liver damage is determined by the bilirubin production level of the case in question but otherwise the urobilinuria is independent of this level.*

Fig.4.

Acute hepatitis,Case 19.

Serum bilirubin————
Urine bilirubin———————
Urine urobilinoid————
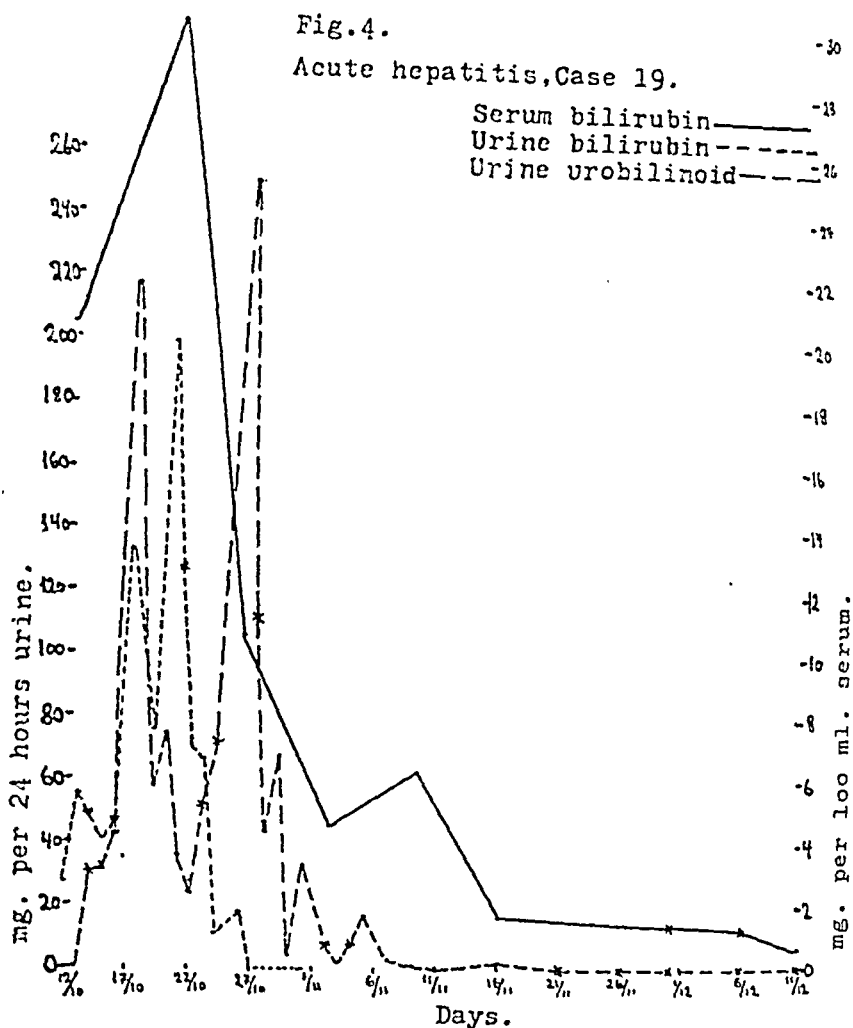
So, it is a simple logical sequel to our explanation of the genesis of jaundice, bilirubinuria and urobilinuria (cf. With, 1944, 8, 9, 10) and the theory of the individual variation of the bilirubin production level (With, 1944, 11) that *quantitative estimation of the urobilinuria is a more reliable indication of the degree of liver damage than quantitative determination of hyperbilirubinemia and bilirubinuria.*

The Urobilinuria in Occlusive Jaundice.

The urinary excretion of urobilinoids in occlusive jaundice is seen from Table 2 and the maximum excretion is summarized in

Diagram 2 in which it is compared to the excretion in hepatitis. The average maximal excretion is seen to be somewhat lower in occlusive jaundice (2.8 mg per 100 ml and 25.6 mg per 24 hrs.) than in hepatitis (3.5 mg per 100 ml and 45.6 mg per 24 hrs.), but the dispersion is so great that the diagnostic value is limited; it seems, however, that values over 50 mg per 24 hours are suggestive of hepatitis but determinations on a greater number of cases of occlusive jaundice are necessary to verify this assumption.

As seen in several of the cases urobilinuria is totally absent both in occlusive jaundice and hepatitis when the flow of bile into the intestine is completely or almost completely interrupted. This is in agreement with the commonly accepted theory of the enterogenous formation of urobilinoids.

In Case 7 there was, however, a certain urobilinuria in spite of total biliary obstruction (»white bile»). This cannot have been caused by bacterial infection of the bile passages (Hildebrandt, 1909; McMaster & Elman, 1926) as the temperature was normal and no signs of inflammation were found at the operation. Another possibility for enterogenous urobilin formation in complete obstruction is extravasation of blood into the intestine (cholemic hemorrhagic diathesis) and transformation of the bilirubin of the serum into urobilin. The patient did not show symptoms of gross hemorrhagic diathesis, but as his serum prothrombin was only 28 per cent of the normal it is not improbable that minor intestinal hemorrhages occurred at the time of the urobilinuria; as benzidine reaction was not carried out on the feces, it is impossible to decide this question with certainty.

On the other hand, it is to be emphasized that a hepatogenous formation of urobilinoid is by no means excluded. French authors thus reckon with a hepatogenous urobilinoid formation (cf. Widal & Abrami, 1928) and also recent German authors are inclined to do so (cf. Halbach, 1938); moreover it is to be looked upon as an established fact that urobilinoids can be formed outside the intestines (cf. With, 1944, 10). But as the hepatic formation of urobilinoids only seems to be found in man during hemolytical crises, it is unlikely that the urobilinuria in our Case 7 should have been hepatogenous. That our case is unique is certain, as Watson (1937) in his great material did not see a single case of complete biliary obstruction with urobilinuria.

The Pathogenesis of Urobilinuria in Occlusive Jaundice.

The pathogenesis and clinical significance of urobilinuria in biliary occlusion (i.e., partial occlusion, as urobilinuria is practically always absent in total occlusion) are worth some closer con

sideration. As urobilinuria is regarded as suggestive of functional damage to the liver one might be inclined to think that its presence indicated simultaneous damage to the liver parenchyma. The rapidity of the disappearence of the urobilinuria after the removal of the biliary obstruction (cf Cases 2 and 6) speaks however against this view.

It is also possible to explain the urobilinuria in partial biliary obstruction without assuming damage of the liver parenchyma. When the outflow of bile becomes difficult, *i.e.*, the pressure in the bile ducts rises, the behavior of the liver cells is different after the height to which the pressure rises (Shafiroff *et al.*, 1939). If the pressure is only a little above the normal (below 25 cm H_2O in dogs) the liver is able to secrete normally against it and the serum bilirubin remains normal; if the pressure is higher, bilirubin appears in the lymph and later in the blood, and the concentration of the bilirubin in the lymph and the serum rises with the pressure till a certain limit is reached. It seems as if the normal secretory mechanism of the liver parenchyma into the bile capillaries is replaced by a secretion into the lymph capillaries, and this mechanism is only capable of transferring a part of the serum bilirubin into the lymph, as the serum bilirubin concentration rises even if the lymph of the thoracic duct is collected and not emptied into the blood stream (cf. also With, 1944, 9).

The behavior of urobilinoids under these circumstances is not investigated, but it is reasonable to assume that the liver cells are not able to excrete urobilin against a greater pressure than that against which they are able to excrete bilirubin. In partial occlusion with urobilinuria and jaundice, *i.e.*, an increase in the bile duct pressure great enough to cause retention of bilirubin and secretion of bilirubin into the lymph but too small to stop its excretion into the bile completely, it is very likely that also a part of the urobilinoid reaching the liver through the portal vein is retained in the serum or secreted into the lymph, while under normal conditions practically all such urobilinoid is disposed of by the liver. In this way urobilinoid reaches the great circulation, and the situation is then the same as in the case of liver lesions in which more or less urobilinoid passes the liver and thus reaches the great circulation.

This theory *explains the urobilinuria in occlusive jaundice* along the same lines as the hyperbilirubinemia is explained (cf. With 1944, 9) and *without assuming hepatocellular damage*. It is to be emphasized, however, that this theory is at present without experimental support, as urobilinoid determinations in the lymph from experimental animals with partial biliary occlusion have not yet been carried out.

Further, it is to be kept in mind that the degree of the urobilin-

uria as well as of the jaundice is also to a certain degree dependent on the bilirubin production level (cf. above).

Variation of Urobilinuria within the 24-hour Period.

As the bilirubinuria may show very great variation within the 24-hour period (With, 1943, 5), we have also determined the excretion of urobilinoids at various times of the day in some of our cases of hepatitis. The results are presented in Table 7.

Table 7.

Variation of the Urobilinuria within the 24-hour Period.

Time interval	Case 6, 11/1	Case 7, 12/1	Case 8, 12/1	Case 10, 20/2	Case 11, 2/3
8—12 hrs. ..	1.92	3.84	1.85	2.95	2.91
12—15 hrs. ..	1.80	4.80	1.72	2.73	3.08
15— 8 hrs. ..	2.30	4.22	0.98	3.38	2.69

The figures are in mg per 100 ml.

The table shows a certain amount of variation but far less than is seen in the excretion of bilirubin with the urine. A determination of the urobilinoid concentration of an arbitrary sample of urine thus gives valuable information if it is impossible to obtain a sample of the 24-hour urine.

The Urobilinuria in Acute Hepatitis.

As seen from Table 6 and Figs. 2, 3 and 4 the urobilinuria in many — if not most — cases of acute hepatitis disappears before the hyperbilirubinemia. This observation is contradictory to the common view, as, *e.g.*, Eppinger (1937, p. 280) states that »auch nachdem der Ikterus wieder völlig abgeklungen ist und die Bilirubinwerte im Serum zum Norm zurückgekehrt sind, findet sich meist immer noch reichlich Urobilinogen im Harn». As mentioned above, Meulengracht observed already in 1919 that hyperbilirubinemia in most cases of acute hepatitis was of longer duration than the urobilinuria. As this observation is now confirmed with reliable analytical procedures there can hardly be any doubt of its

correctness. As urobilinuria nevertheless in some cases lasts longer than the hyperbilirubinemia it is necessary to follow both in all cases.

The Transition from Bilirubinuria to Urobilinuria in Acute Hepatitis.

In most cases of acute hepatitis — with the exception of the slightest — the serum bilirubin in the initial stages reaches a level which lies above the renal threshold, and bilirubinuria develops. In some cases the damage to the liver parenchyma is so severe that the flow of bile into the intestine is more or less completely arrested, and in such cases little or no urobilinoid is formed in the intestine and urobilinuria is absent. In other cases the bile flow is only reduced to a lesser degree and reasonably great amounts of urobilinoids are produced in the intestine and transported to the liver with the portal blood; as the liver parenchyma is not capable to dispose of all this urobilinoid as under normal circumstances and some urobilinoid may also reach the blood via the deranged bile capillaries and the lymph, the urobilinoid passes into the great circulation and is excreted with the urine. In cases of the first-mentioned nature — almost complete cessation of the bile flow — there comes during the process of healing a time when the bile flow increases, more urobilin is formed, and urobilinuria appears.

According to this theory of the pathogenesis of urobilinuria and bilirubinuria — for a more detailed discussion of this and other theories see With, 1944, 9 and 10 — several combinations are possible in acute hepatitis: *1.* The mildest cases, with low bilirubinemia, and urobilinuria without bilirubinuria. *2.* Cases with bilirubinuria and urobilinuria both present from the beginning (and disappearance of the bilirubinuria before the urobilinuria). *3.* Cases with only bilirubinuria in the beginning and later urobilinuria (either present for some time simultaneously with bilirubinuria or developing at the time when bilirubinuria disappears).

One might think that the relative intensity of bilirubinuria would be indicative of the severity of the liver damage, and this is, presumably, also true in cases with the same bilirubin production level; but if nothing is known of this level the intensity of bilirubinuria is only of limited value as an expression for the liver da-

mage. Cases of type 1 therefore may show relatively intense liver damage if the bilirubin production is low. Extreme cases of this sort are such of acute yellow atrophy of the liver without jaundice (cf. Eppinger, 1937, p. 310); also the so-called »icterus catarrhalis sine ictero» may belong to this type. If low values for the serum bilirubin accompanied by relatively high urobilinoid excretion are found from the beginning, it points to a rather severe hepatitis in an individual with low bilirubin production. Several cases of type 1 are found in our material (Cases 14, 15, 18, 20, 24, 25, 26, 27) but only Case 26 showed relatively great — but rapidly transient — urobilinuria.

Cases of type 2, in which both bilirubinuria and urobilinuria were present at the height of the disease, are represented by our Cases 5, 10 and 23. Case 10 was a mild one while the other two — unfortunately only observed a short time — presumably were moderate ones. If the bilirubinuria and hyperbilirubinemia are moderate and the urobilinuria pronounced, a case of this type is to be regarded as severe, as this is indicative of a moderate bilirubin production with intense urobilinuria as measured relatively. In such cases, however, determination of the fecal urobilinoid — after the disappearance of the jaundice — is desirable to confirm the low bilirubin production.

Cases of type 3 seem to be the most common; in Cases 1, 8, 9, 11, 21, 22 and 30 the bilirubinuria disappeared and was replaced by urobilinuria, and urobilinuria and bilirubinuria were only simultaneously present for a few days.

This is very instructively illustrated by Figs. 1 and 3 in which the urinary bilirubin excretion also shows good parallelism to the serum bilirubin. That such a parallelism is by no means always found is evident from Figs. 2 and 4, and this is also reasonable, as the bilirubin excretion is determined by the kidney function as well as by the serum bilirubin concentration.

The rapid fall in the serum bilirubin and the bilirubinuria which in so many cases precedes the urobilinuria may be somewhat difficult to explain if the variations in the hyperbilirubinuria are looked upon as caused only by the damage to the liver cells themselves; one would hardly expect such rapid variations in the alterations of the parenchyma cells in the course of the disease. The explanation of this rapid fall in the serum bilirubin is presumably the regression of the inflammatory oedema of the liver and the compression of the fine bile ducts caused by it, as changes in inflammatory oedema may take place rapidly. Thus our observations give support to the

view of Eppinger (1937, p. 117) that »intrahepatic mechanical jaundice« plays a part in the pathogenesis of the jaundice in hepatitis.

In all our cases belonging to type 3 the bilirubinuria disappeared rapidly — in a few days — after the urobilinuria had appeared, with the exception of the severe Case 19 (Fig. 4).

In this case the observation was begun two days before the urobilinuria appeared and the patient was at this time very ill with high fever (39—40°), prostration and acholic feces. In the 24 hours from 13. to 14. 10. the urobilinuria commenced and the feces became colored, but there was at that time no amelioration in the clinical condition which only gradually grew better in the following week. It is interesting that the serum bilirubin and the bilirubinuria showed an increase at the time the urobilinuria commenced. Perhaps an increase in the bilirubin production took place at this time or perhaps the urobilinoid excretion in this case was partially hepatogenous. Otherwise this puzzling finding may hardly be explained. The case showed a very high urobilinoid excretion which seems to indicate a severe liver damage (250 mg per 24 hours reached).

The transition of bilirubinuria into urobilinuria discussed takes place when the hepatitis is regressing. It is possible, however, that the opposite process — i.e., urobilinuria going on to bilirubinuria — takes place in the initial stage of the disease.

In most descriptions of the clinical picture of acute hepatitis (»catarrhal jaundice«), and in several of the histories of our cases as well, it is mentioned that the patient often has observed dark urine some days before the jaundice appears. As bilirubinuria is only seen with relatively high serum bilirubin concentrations, it can hardly be assumed that the dark urine in these cases should be due to bilirubinuria — if not the serum threshold for bilirubinuria should be lower with rising than with decreasing serum bilirubin. Consequently, it is reasonable to assume that urobilinuria should precede bilirubinuria in such cases and that the initial dark color of the urine should be due to urobilin.

As it is very seldom that cases are under clinical observation in the initial stages of a hepatitis, observations on such cases are scanty. Some observations supporting the above-mentioned view are reported by Hallgren (1942, p. 87—89) who — during investigations of a local epidemic of hepatitis — regularly found urobilinuria (Schlesinger reaction) before jaundice became visible, while bilirubinuria (iodine test) was present first after jaundice had appeared. In our Case 31 the urine was unfortunately not analysed the first day of the disease and the serum not before the third day.

The Urobilinuria in Chronic Hepatitis.

The urobilinuria in chronic hepatitis is seen to be very variable (Table 4). In the two cases with intense jaundice and bilirubinuria

(Cases 2 and 7) the excretion of urobilinoid with the urine was only small, presumably because only small amounts of bilirubin reached the intestine. So, in Case 7 the excretion of urobilinoids with the feces was only 7.2 mg per 24 hrs (in the period 8.—12. 10). In the other cases the urobilinuria as a rule was only a little above the normal limit and therefore not of much diagnostic value, but in Case 4 an intense urobilinuria was found although the serum bilirubin was only moderately elevated and bilirubinuria absent. This case was a very grave one, as the patient died a few weeks later in hepatic coma. So it seems reasonable to conclude that the finding of great urobilinoid excretion with the urine in cases of chronic hepatitis is a bad prognostic sign; on the other hand, almost normal — or perhaps entirely normal — urobilinoid excretion is often found in chronic hepatitis. The question whether hyperbilirubinemia or urobilinuria is the most sensitive indicator of functional liver damage in chronic hepatitis cannot be solved from our material.

The Fecal Excretion of Urobilinoid.

The fecal urobilinoid has only been determined in some of the cases in this material. In the clinic of jaundice and liver diseases such determinations are chiefly of interest in the diagnosis of hemolytic jaundice and as a means to determine whether a biliary obstruction is complete or not. Watson (1937, 1910) — using the same method as we with minor differences — found between 40 and 280 mg per 24 hours in 17 normal persons; in complete biliary obstruction he always found below 5 mg and most often below 1 mg per 24 hours. In partial obstruction and reduced bilirubin excretion due to hepatitis he also found low values, but in most cases above 5 mg per 24 hours. In hemolytic jaundice he found 300—2500 mg per 24 hours.

Our investigations on the urobilinoid excretion in normal persons are given in Table 5. All the subjects used showed regular daily stool and the 24-hour excretions given are all calculated as means of determinations made in a 4 × 24-hour period; in this way variations due to irregularities of defecation are eliminated (cf. Watson, 1937). We found the same considerable variation as Watson, i.e., 25.1 to 225 mg per 24 hours; this variation is, at least

partly, an expression of the individual variation of the bilirubin production (cf. With. 1944, 11).

Our observations in the pathological cases are also in agreement with those of Watson. Case 7 of occlusive jaundice (complete obstruction) showed an excretion of only 1.4 mg per 24 hours (7.—11. 12), Case 1 (partial obstruction) 11.2 mg per 24 hours (19.—23. 11.), and Case 3 only 0.92 mg per 24 hours (13.—17. 12.); accordingly the obstruction has to be considered as total in Case 3. That urobilinoids — even traces — are found in complete obstruction is difficult to understand but is explained by the desquamation of bile-stained epithelial cells into the intestine and occasional small bleedings of exudation of serum which is rich in bilirubin in these cases (Watson, 1937, 1940). The variations of fecal urobilinoid in hepatitis are also illustrated by determination in some cases; in Case 6 (acute hepatitis) the following excretions (mg per 24 hours) were found: 9.—13. 1. 12.2 mg; 13.—17. 1. 37.5 mg; 17.—21. 1. 58 mg; 21.—25. 1. 62.3 mg (the corresponding values for the urinary excretion are seen from Table 3). Case 7 showed 9.—13. 1. 37.5 mg; 13.—17. 1. 158 mg; 17.—21. 1. 89 mg; 21.—25. 1. 182 mg; 25.—29. 1. 142 mg; 29. 1.—2. 2. 202 mg. Case 8 gave the values 5.—9. 1. 15.8 mg; 9.—13. 1. 31.1 mg; 13.—17. 1. 44.3 mg; 17.—21. 1. 40.2 mg; 21.—25. 1. 55.7 mg. Finally, Case 11 showed 22.—26. 2. 9.1 mg; 26. 2.—2. 3. 7.1 mg; 2.—6. 3. 69 mg; 6.—10. 3. 114 mg. The rapid rise from ca. 7 to 69 in this case has, possibly, taken place more gradually in the course of the 4-day-period covered by the determination 2.—6. 3. In Case 7 of chronic hepatitis the fecal excretion was 7.2 mg per 24 hours in the period of 8.—11. 10.

These determinations do not seem to give any information of clinical value; they may give some information concerning the bilirubin production, but not of its actual value as the fecal urobilinoid can only be used as an expression for the lower limit of the bilirubin production (With, 1944, 11). Further, a drawback of the determinations in feces is that more rapid variations cannot be followed as one has to analyse 4 × 24-hour portions. So, the clinical use of determinations of the fecal urobilinoid in jaundice and liver diseases is limited to the diagnosis of hemolytic jaundice and the decision of whether an occlusion is partial or complete.

The so-called »urobilin quotient« (Adler & Sachs) is the 24-hour urinary urobilinoid expressed in per cent of the 24-hour fecal urobilinoid. Its normal values are seen in Table 5. It can be calculated for the cases of hepatitis in which the fecal excretion was determined. It is seen to be greatly increased in hepatitis (and partial occlusion) with urobilinuria. It is open to question whether this »quotient« is of more clinical value than simple determination of the urobilinuria. As the analytical work involved in its determination is more than twice the work necessary for the determina-

tion in the urine alone and the fecal excretion can only be determined with reasonable accuracy in 4-day periods, it seems unlikely that the *quotient* should gain more extensive use in clinical work.

Summary.

Quantitative determinations of the serum bilirubin, the urinary excretion of bilirubin and urobilinoids and in some cases the fecal excretion of urobilinoids were carried out in hemolytic jaundice (Table 1), occlusive jaundice (Table 2), acute and chronic hepatitis (Table 3 and 4) and in normal persons (Table 5).

It is pointed out that the serum bilirubin concentration in jaundice is not determined solely by the pathologic process causing the jaundice, but also by the bilirubin production level characteristic of the patient in question. The urobilinuria, contrary to the hyperbilirubinemia and bilirubinuria, is not influenced by the bilirubin production with the exception that the bilirubin production level determines its upper limit.

The amount of bilirubin and urobilinoid excreted with the urine is of no aid in differentiating occlusive jaundice from hepatitis, with the possible exception that an excretion above 50 mg per 24 hours seems to point strongly to the diagnosis of hepatitis. The urobilinuria in occlusive jaundice seems to be a simple sequel to the occlusion and is not necessarily due to simultaneous damage to the liver parenchyma.

The hyperbilirubinemia is in most cases of acute hepatitis a more sensitive expression for the state of the liver parenchyma than is the urobilinuria — in contradiction to the prevailing assumption.

The relation of urobilinuria to bilirubinuria is discussed with remarks on their pathogenesis in different forms of jaundice.

The clinical value of determination of urobilinoids in the feces is exemplified and discussed. Its main value in the clinic of liver diseases lies in the diagnosis of complete biliary (neoplastic) occlusion.

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From the Medical Clinic at Lund, Sweden (Director: Professor
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Diplegia Facialis.

By

STIG RADNER.

Since Sir Charles Bell in 1829 proved that facial paralysis
depended on the cessation of the function in nervus facialis expe-
riences about the various lesions that could produce such a para-
lysis were gradually gathered. The clinical differentiation in peri-
pheral and central facial pareses was introduced in the diagnos-
tics in 1862 by Armand Trousseau, who thus gave the etiologic
discussion a more favourable starting point.

At the beginning of this century we already had an important
casuistic material of peripheral facial pareses. For historical rea-
sons this material, however, was not subjected to such investiga-
tions as we nowadays consider to be the condition of a modern
etiological analysis; lumbar puncture and x-ray examination had
not yet been included in the routine examination of neurological
cases. One could, however, separate a group of surgical paralyses
caused by injuries to the nerve through tumours, purulent otites,
fractures, or direct trauma, from a larger group of medical paraly-
ses, the etiology of which mostly seemed unclear or was considered
»rheumatic».

In the last decades no greater compilation of peripheral facial
pareses has been published, but on the other side the cases that
we have encountered in the literature have as a rule been examined

in a satisfactory manner. What has been brought forth through the more modern casuistics is above all the symptomatic character of the medical facial paresis; it has become more and more obvious that this paresis should not *a priori* be considered as a wholly independent disease but rather as a part symptom of a more or less widespread affection of the central nervous system. A number of different meningo-encephalo-myelitic conditions could occur as a pathogenetic factor.

Of these should in the first place be mentioned those originated by virus: poliomyelitis acuta, encephalitis lethargica, zoster, and parotitis epidemica. But also bacterial and luetic processes in the central nervous system could even occur with monosymptomatic facial paresis of peripheral type. It is furthermore known that sclerosis disseminata sometimes begins with such a paresis; this can then be fully restituted, only to reappear at the next relapse of the disease as an initial symptom. Finally the peripheral facial paresis occurs together with polyneuritis of various genesis but specially with a type that has many denominations and i.a. is called »acute febrile polyneuritis» (Osler), »infective neuronitis» (Foster Kennedy) or »polyradiculitis acuta» (Mogens Fog, H. C. A. Lassen); another term is polyneuritis with facial diplegia, indicating that the double paresis belongs to the more constant symptoms of the disease. With the Scandinavian authors we shall below use the term polyradiculitis acuta.

Now it is known for a long time that the distinction of diseases in the central and in the peripheral nervous system in certain cases mainly has a didactic basis. Already Babinski writes »que bien des agents qui déterminent des névrites provoquent à la fois une perturbation du système nerveux central et du système nerveux périphérique». But this thesis does not earlier seem to have been practised in regard to facial pareses.

From these general etiologic points of view it should be evident that patients with facial paresis not seldom also show other neurological symptoms of a character that changes from case to case. It is the same in the cases of bilateral paresis which will be described below. These other symptoms could of course completely dominate the picture, while the facial paresis occurs as a less outstanding, perhaps terminal phenomenon. Such forms do not occur in the present casuistics. The choice has been made accord-

ing to the principle that only those cases are included where the double paresis has been a clinical main symptom and a reason for the admission.

It is obvious that on the part of the scale poly-monosymptomatic facial pareses, where symptoms are more scarce, forms may appear where we are unable, with our present methods of examination to show a supposed co-reaction of the central nervous system and its membranes. In these separate cases the etiologic reasoning must be hypothetical; it is here the »rheumatic» genesis was inaugurated. It does not seem unbelievable that even the after careful analysis exclusively monosymptomatic facial paresis of peripheral character represents a »forme fruste» to one in other cases more manifest meningo-encephalo-myelitis process.

The intention with this work is partly to publish a material of medical facial diplegias examined in our special department, partly with the help of this material and from data in the literature to find out whether diplegias and monoplegias reveal mutual differences in regard to etiology and healing result. It should already now be pointed out that fundamental differences in this regard have not been found. As to the etiology this corresponds fully with earlier published experiences; comparisons in regard to the restitution do not seem to appear in available literature. If consequently the two forms of paresis do not differ in regard to *quality* they, however, show a *quantitative* divergence.

We will now examine the material.

The material.

This includes 8 cases of double peripheral facial paresis that during the last 15 years, 1929—1943, have been attended to at the Medical Clinic at Lund.

To the casuistic description is added a short epicritic discussion of the individual case.

Case 1. 754/1929. Worker's wife, aged 58, admitted on April 4, 1929. Sickness started at the end of Feb. 1929 with paresthesias and weakness in both hands. On Feb. 26, at first weakness of the arms and later a sudden paralysis of same and of the left leg, which refused to support the patient. After a week in bed these pareses disappeared almost completely but on a morning three weeks before admission they were succeeded by a double paralysis of the face.

Status. On examination of the patient a total peripheral double facial paresis was found but otherwise nothing clearly pathological in the nervous system. Lumbar puncture made six weeks after the disease had set in showed 2.2 lymphocytes and 0.3 leukocytes per cubic millimeter. The Nonne and Pandy reactions were negative. The Wassermann reaction of the fluid was negative. The patient was in the beginning subfebrile and the last week afebrile. The blood pressure was 135 systolic. After slight improvement the patient was discharged on May 15, 1929.

Readmitted on March 14, 1931, on account of an acute liver disease. The patient then had an important deficiency status in both nervi faciales: »Cannot completely close rimae oculi and only partly show the teeth«. Died of parenchymatous liver degeneration after a couple of days. The pathologic-anatomic examination of the brain and its membranes showed, in addition to slight senile changes, normal macroscopic conditions.

Epicritic discussion. This case undoubtedly represents the type of general central nervous affection which is called polyradiculitis acuta or polyneuritis with facial diplegia. It is characteristic of this disease that the extremities are first stricken, as a rule beginning with the lower ones; the picture then appears as a Landry's paresis. The facial paresis occurring somewhat later is nearly always double.

Guillain, Barré and Strohl published in 1916 two cases with »un syndrome de radiculo-névrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire«, of which the one case showed a double facial paresis. Even the other symptomatology in these both observations justifies the introduction of the syndrome in the same nosological group as polyradiculitis acute. While the fluid analysis in the afore-mentioned publication showed a pronounced increase of the albumin without cell reaction, the result of the analysis has in other cases varied considerably; certain authors state a quite normal cerebrospinal fluid, others a pathological increase of the cells with or without a simultaneous hyperalbuminosis. (Cf. Taylor and McDonald, Mogens Fog and C. H. A. Lassen.)

Case 2. 1594/1931. 27 years old bricklayer. Admitted on July 28, 1931. Fell ill 2 weeks before entrance with ache in the right part of the head together with dizziness. On July 24, right-sided paralysis of the face. Was admitted to the clinic on account of increased dizziness and vomiting.

A few days after admission the patient also got a left-sided facial paresis.

Status. On examination a double facial paresis was established. Furthermore one found vestibulary symptoms in the form of nystagmus when looking to the right, a tendency to fall to the left and unsteady gait. A caloric test gave no certain pathological result. Lumbar puncture made a fortnight after the beginning of the disease showed 0.6 lymphocytes and 0 leukocytes per cubic millimeter. The Bisgaard test, positive up to 1/30. Wassermann in fluid, negative. Was the whole time lying afebrile. Other examinations gave normal results. The patient left the hospital on Sep. 15, 1931. He had then still total paresis on the left side but was somewhat improved on the right side.

The post-examination made in 1943, 12 years after the beginning of the disease, showed that considerable rests of the facial pareses still remained. The patient could only with great difficulty close rimae oculi on both sides; he was unable to point the mouth and whistle. The defects appeared most distinctly on the left side.

Epicritic discussion. The time for the beginning of the disease (July) and the remaining status of deficiency might *in casu* point toward poliomyelitis. This etiologic possibility is, however, contradicted by the fact that the left-sided paralysis appeared without cell reaction in the fluid and during an afebril stage. The high concentration of albumin in the cerebrospinal fluid together with the absence of pleocytosis seems rather to point to an affection of the same kind as in the preceding case, then closest to the Guillain-Barré-Strohl variation, though as a syndrome fragment in the now actual observation.

Case 3. 31 years old officer in the air force. Admitted on Jan. 13, 1934. Fell ill in the beginning of Nov. 1933 in angina, bronchitis and fever. He continued, however, his service and thereby got exposed to very cold weather. On Nov. 6, 1933, he was however compelled to go to bed and during the next 2 days a double facial paralysis developed. For the nearest time the patient was cared for in another hospital and here the left-sided paresis was completely restituted while the right one remained. Was brought over here on suspicion of encephalitis. Lumbar puncture had not been made.

Status. On examination a right-sided peripheral facial paresis was observed. The patient could not close rima oculi and not wrinkle the forehead on the right side. The left facialis had undergone a complete restitution. Neurologically everything was normal with the exception of a slight anisocoria (the left one larger than the right one). Lumbar puncture made 2 months after the onset of the disease showed normal conditions. Wasserman test in fluid, negative. Discharged after 2 days.

The post-examination 1943, 10 years after the beginning of the disease, showed on the right side a slight but clear contracture within the region of the lower facialis branch with drawn up corner of the mouth and strongly marked naso-labial line. On the left side normal conditions.

Epicritic discussion. On account of lack of information conccin-
ing the cerebrospinal fluid during the acute stage of the disease,
it is difficult to form an opinion about the etiology in this case.
It might lie close at hand to use the term »paralysis a frigore» or
»rheumatic», but the cooling off might be of secondary importance
in relation to the previous infection; this might possibly have occur-
red with a reaction in the central nervous system, which reaction
with the exception of the facial paresis has been latent.

Case 4. 866/1935. 42 years old seamstress. Admitted on March 13,
1935. Fell ill in Dec. 1934, with nasal catarrh and cough and at times
pain in the left shoulder. After a week the right eye turned strongly red.
This was restituted after 3 days but was than followed by a right-sided
facial paralysis. At the same time the sense of taste decreased. The patient
felt dizzy and unwell and had a subfebrile temperature. In another week
a paresis of the left half of the face also developed. A few days later the
patient also got girdle pains first in the left thorax half and later also in the
right one; these pains were accompanied with a slight local swelling and
hyperesthesia. The patient was admitted as a consultation case from
another hospital.

Status. On examination, a double peripheral facial paresis was found,
total on the left side; only a slight mobility on the right side. Otherwise
there were no remarks to be made about the motorics of the skeleton
muscles. In a girdle-formed region around the circumference of the trunk
corresponding to the dermatomeres Th IX — Th XI there was a diminu-
tion of the sensibility. On ophthalmoscopic examination one observed on
both sides a pale papillo-edema with its greatest protrusion on the left
side. Examination of the visual fields with a red object showed an indica-
tion of scotoma in the right upper quadrant. A fortnight later the papillo-
edema had diminished considerably; the scotoma had then disappeared.
The visus was 1 oc. amb. The nervous system otherwise on the whole
normal. Suboccipital puncture carried out 3 months after the bginning
of the disease showed 10 lymphocytes and 2.8 leukocytes per cubic milli-
meter. The Nonne and Pandy tests, negative. The Wassermann test of
fluid, negative.

Patient was all the time lying subfebrile. Sedimentation rate at the
most 13 mm/1 hour.

Discharged on May 3, 1935, with objectively the same status, with the
exception of the afore-mentioned improvement of the condition of the
eyes.

The post-examination that was made in 1942, 8 years after the onset of
the disease, showed a considerable state of deficiency in both nervi facia-
les. The patient had a rigid face expression. She could only slightly abduct
the corners of the mouth or wrinkle the forehead. She could not fully close
rimae oculi. The patient moved slowly and the gait was stiff and some-

what lingering. The superficial sensibility was normal. Ophthalmoscopically a beginning opticus atrophy was proved. Visus had gone down to 0.5 oc.amb. In the spinal-fluid 4 lymphocytes and 1 leukocyte were found per cubic millimeter.

Epicritic discussion. In all probability this case could etiologically be allocated to the nosological group of encephalomyelites which is called encephalitis lethargica. The stiff general motorics 8 years after the onset of the disease point to this. One can, however, not altogether disregard a polyradiculitis acuta which has healed deficiently.

Case 5. 2634/1939. 12 years old schoolboy. Admitted on Oct. 24, 1939. Fell ill in nasal catarrh 1 month before admission, with ensuing ache between the shoulders radiating upwards toward the occiput. Three weeks before the admission a double paralysis of the face gradually developed.

Status. On examination, a bilateral peripheral facial paresis was found here. Only slight mobility in the facial muscles. Could not show teeth and not wrinkle the forehead. Rimae did not close completely. Lumbar puncture that was made 1 month after the beginning of the disease, showed 136 lymphocytes and 10 leukocytes per cubic millimeter. The Bisgaard test, positive up to 1/10. The Wassermann test of fluid, negative. Later lymphocytes decreased to 14 and leukocytes to 1 per cubic millimeter. The patient was the first week lying subfebrile, thereafter afebrile. Sedimentation rate was 10 mm/1 hour.

When discharged the facial diplegia was unchanged.

The post-examination in 1943, 4 years after the beginning of the disease, showed still an important state of deficiency in both nervi faciales. The patient could then not point the mouth and just barely show the teeth. But rimae oculi were fully closed and with the same strength on both sides.

Epicritic discussion. In this case the facial diplegia was thus the only exterior signal of the inflammatory state in the central nervous system. The paresis in both facial regions remaining after 4 years is an evidence of the profound nature of the inflammation, and these was most likely a nuclear injury. The pronounced lymphocyte reaction in the fluid makes one think of a virus affection, possibly of the same kind as in poliomyelitis or parotitis. In both these diseases monosymptomatic peripheral facial pareses have been described. The time for the onset of the illness in this case (Sep.) may correspond with the assumption of such an etiology.

Case 6. 2336/1941. 29 years old merchant's wife. Admitted on Oct. 9, 1941. Illness began on Sep. 20, 1941, with tenderness of the soft parts of the gluteal regions, upper arms and shoulders. After a week a double facial

paralysis gradually developed. Later increasing tenderness of the soft parts and headache. Admitted as a consultation case from another hospital.

Status. On examination, a peripheral total facial diplegia was proved. Otherwise the neurological conditions were normal. The spinal fluid analysis showed no cell reaction but the Nonne and Pandy tests were positive and the Bisgaard test positive up to 1/50. A month later the Bisgaard test was positive up to 1/20. The Wassermann reaction of the fluid, negative.

Discharged on Sep. 13, 1941, with unchanged total bilateral facial paresis.

The post-examination in 1943, 2 years after illness started, still showed considerable remainders after the pareses. The paralysis had been total for about 6 months, after which time a certain mobility had developed in the left corner of the mouth.

Epicritic discussion. Specially two features of the disease picture should be pointed out: the palpation tenderness in the soft parts and the heavy increase of albumin in the fluid. Guillain, Barré and Strohl paid in their publication a great deal of attention to both these phenomena, which are included as components in the syndrome named after these authors. In this case there were no pareses of the extremities, but in all likelihood it was nevertheless here a case of a fragment of the bigger meningo-encephalo-myelitis syndrome: polyradiculitis acuta.

Case 7. 2570/1941. 25 years old farmer's wife. Admitted on Nov. 28, 1941. Earlier now and then headache of varying localization. Fell ill about Nov. 23, 1941, with fever, 39.8 degrees, and ache in the right side of the occiput, with indisposition and vomiting. In this connection the patient developed a right-sided paralysis of the face. On the previous day the patient had been out in cold weather and draught. A few days before admission spasms in the right eye-lid together with flickering before the eyes and photopsies.

Status. On examination, a total right-sided paresis was found and after a few days in the ward even a left-sided paresis of peripheral type then started to develop. The examinations gave otherwise a normal result. The spinal fluid showed no changes. The patient was lying afebrile the whole time. The sedimentation rate was 8 mm/1 hour. Blood pressure 120/80.

• On discharge Dec. 12, 1941, the left-sided paresis remained unchanged while the right-sided one was decreasing.

The post-examination in 1943, two years after the onset of the disease, showed that a complete restitution had taken place. »A certain rigidity in the right half of the face» could, however, make itself noticeable at the exposure to cold weather or draught. On these occasions the also suffered from a severe headache.

Epicritic discussion. The manifest state of infection at the beginning of the disease must be considered of decisive importance for the genesis of the disease, even if no reaction from the nervous system in the form of changes in the spinal fluid has appeared. The absence of changes in the fluid can then point to a mild. less farreaching central nervous affection, which can explain the comparatively rapid restitution in the present case.

Case 8. 2309/1942. 32 years old dairyman. Admitted on Sep. 26, 1942. Illness began on Aug. 25, 1942, with diarrhoeas thin as water, and fever about 39 degrees. A week later increasing ache in occiput, back and thighs. After the high-febrile period in the beginning of the disease patient was lying subfebrile. Two days before admission a left-sided facial paresis developed.

Status. On examination, a total peripheral facial paresis was found and a couple of days after the admission a right-sided paresis of the same nature developed. The corneal sensibility on both sides was diminished. With the exception of an occipital rigidity of moderate degree the neurological conditions were otherwise normal. The analysis of the spinal fluid showed 150 lymphocytes and 52 leukocytes per cubic millimeter. Bisgaard test, positive up to 1/50. Wasserman test of fluid, negative.

Patient was lying subfebrile the first month; thereafter afebrile.

On discharge Nov. 17, 1942, both nervi faciales were still paretic with the exception of a beginning slight motility in the right corner of the mouth.

The post-examination. During the following months the patient returned still six times for control and a slowly progressing restitution of the facial paresis could then be noticed. At the last admission, in Feb. 1944, 19 months after the beginning of the illness there were, however, still considerable residues. The mimics were stiff. The patient could not wrinkle the forehead to the full extent, but somewhat more on the right side than on the left one. Rimae oculi could be closed but with poor strength. In attempting to point the mouth considerable rigidity was still encountered in the corners of the mouth. — The corneal reflexes were now again normal. — The examination of the spinal fluid showed normal conditions.

Epicritic discussion. Hardly any other disease than poliomyelitis could be mentioned as an etiological basis for the described picture of the symptoms. The acute illness with diarrhoea and fever, later on meningitic irritation, pareses of peripheral character and the pronounced lymphocyte reaction of the spinal fluid speak decidedly in favour of this etiology. The slow and incomplete restitution has the same diagnostic value.

The peripheral monosymptomatic facial paresis in poliomyelitis has been described by a number of authors, from Sweden i.a. by Wallgren, who points out that already Medin stated these more

abortive forms of the disease. The frequency of facial pareses in poliomyelitis has under different epidemics varied between 3.8 and 12 percent; these figures do not, however, solely include the mono-symptomatic forms.

General Discussion of the Material.

As to the casuistic view on the material it could here be mentioned that in the Scandinavian literature thus far there only seems to be a small paper on this subject: Vagn Askgaard has in 1920 described two cases of double peripheral facial paresis (»2 Tilfaelde af dobbeltsidig perifer Facialisparese»). In other available literature during the last decades we vonly find lesser casuistic contributions without accounts of the healing results.

To the extent conclusions can be drawn from our limited material no fundamental etiological differences seem to arise on comparison between this material on the one side and the literary data concerning unilateral facial pareses on the other side. From published casuistics it is, however, evident that a distinct quantitative divergence in etiological respect can be proved in two different diseases: polyradiculitis acuta and zoster. Bradford, Bashford and Wilson (1918) thus found that in 17 cases of »acute infective polyneuritis» with facial paresis 14 cases showed facial diplegia of peripheral type; the paresis was only in three cases unilateral.

Zoster on the other side practically always occurs with unilateral pareses. Sure cases of diplegia have not been described.

In connection with the etiological discussion there is a special interest for the discoveries in the cerebrospinal fluid: do, in this respect, mono- and diplegias act in a different manner? For lack of available data from earlier literature concerning analysis of the fluid in unilateral pareses the Medical Clinic's material of such pareses covering the period 1928—1943 (the same time as for the bilateral) has been examined in regard to the fluid. This material consists of 57 cases, of which fluid examination has been made in 34 cases. Quite normal result in the analysis was found in 23, while pathological fluid with increase of cells or/and hyperalbuminosis was discovered in 11 cases. The proportion of the pathological results, of examination is surprisingly large; here one should, however, take due regard to the fact that it concerns hospitalized cases, which possibly represent a selected material of a more alarming

kind. If we now adopt this figure as a representative one (pathological cerebrospinal fluid in one third of the cases) the difference between unilateral and bilateral pareses in this respect becomes rather great: of the 8 facial diplegias in our material there was pathological fluid in 5 cases. On account of the paucity of the material these figures can not of course be considered to be decisive.

The most pronounced quantitative difference between mono- and diplegias seems to lie in the restitution. On post-examinations that have been made on all patients in our diplegia material after longer or shorter time, in different cases from 12 years to 19 months after the beginning of the disease, objective residues have been established in 7 of the 8 cases. In 6 of these (cases 1, 2, 4, 5, 6, and 8) there was a pronounced condition of deficiency in both nervi faciales. In one case a small contracture remained after ten years.

Now we have no statistical data as to the restitution conditions of unilateral pareses, but one might assume that at least half of them undergo restitutio ad integrum.

Summary.

1. The intention of this work is partly to publish a material of medical peripheral facial diplegias examined in a special ward; partly with the help of this material and of data in the literature to establish, whether diplegias and monoplegias show mutual differences in regard to etiology and healing result.

2. After a general survey of etiologic questions a material of 8 facial diplegias, the etiology of which is being discussed, will be presented. Polyradiculitis acuta, encephalitis lethargica, poliomyelitis acuta or other virus inections in the central nervous system have been the probable cause of the disease in six of the eight cases. In the two remaining cases there was an initial infection status, which is considered to be of etiologic importance.

As all these etiologic factors also could give rise to unilateral pareses, a fundamental difference in this respect between the two groups could not be established.

3. Of the eight facial diplegias five had pathological changes in the spinal fluid; in two cases (2 and 6) hyperalbuminosis without cell reaction.

Of 34 fluid-analysed cases with unilateral peripheral facial pareses from the material of the clinic 11 cases had pathological spinal fluid.

On account of the paucity of the material these figures cannot be considered to be decisive.

4. On post-examinations that have been made in all 8 cases of facial diplegia after longer or shorter time in different cases from 12 years to 19 months after the beginning of the disease, objective residues have been established in 7 of the cases. In six of these (cases 1, 2, 4, 5, 6, and 8) there was a pronounced state of deficiency in both nervi faciales. In one of them (3) a smaller contracture had developed after 10 years.

Now there are no statistical data as to the restitutional conditions of unilateral paresis, but one might assume that at least half of them show restitutio ad integrum.

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Vorstand Prof. Dr. K. O. Renkonen.

Über das Vorkommen von Malaria in Finnland.

Von

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(Bei der Redaktion am 7. Juni 1944 eingegangen).

Über die Malaria in Finnland sind in dem 18. Jahrhundert die Arbeiten von Haartman und Radloff, im 19. Jahrhundert die von Ilmoni, Stigzelius, Hjelt und Sievers, und in diesem Jahrhundert die von Sivén erschienen. Das alles ist ein Zeugnis der einstmaligen Aktualität der Malariaprobleme in Finnland. Obwohl uns die damaligen genauen zahlenmässigen Angaben über die Malariafrekvenz fehlen, gibt es doch Daten (Sievers) über die Anzahl der Todesfälle. Das Maximum wird vom Jahre 1820 berichtet. In diesem Jahre starben 1,044 Leute an Malaria. Schätzungsweise lässt sich die gesamte Anzahl der Fälle in den schwersten Epidemiejahren auf etwa 20,000—40,000 vermuten, was sehr viel ist, wenn man es mit der gesamten Einwohnerzahl Finnlands vergleicht, die im Jahre 1820 1,177,500 betrug. Zum Beispiel sei auch erwähnt, dass aus dem Jahre 1862 in den jetzt fast ganz malariafreien Bezirken um die Städte Mikkeli und Joensuu je 4,000 Fälle rapportiert worden sind.

Erst nach dem Jahre 1891 können genauere Daten über die Malariafrekvenz angegeben werden. Diese aber sind bis zum Jahre 1907 mangelhaft, weil nur die Stadtärzte regelmässige Berichte darüber gaben. In den Städten wohnte etwa ein siebentel der ganzen Bevölkerung. Von dem Jahre 1907 an sind alle Fälle prinzipiell der Medizinalverwaltung gemeldet worden. Folgende gra-

fische Darstellung gibt über die Fälle in Finnland, und gleich-
zeitig auch über die Fälle in Schweden eine Übersicht. Die Kurven
sind also auf Grund der offiziellen Statistik berechnet und umfassen
17,575 Fälle aus Finnland in den Jahren 1892—1. 9. 1943 und
sämtliche 128,972 offiziell gemeldeten Fälle aus Schweden aus
den Jahren 1861—1940.

Das Vorkommen von Malaria in Finnland und Schweden.
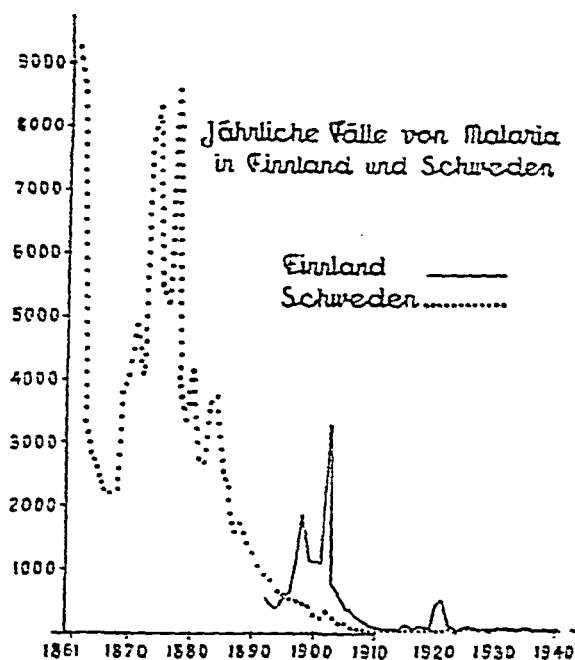
Kurve 1.

Wie ersichtlich scheint die Malaria eine aussterbende Krankheit
sowohl in Schweden als auch in Finnland zu sein. Die Anzahl der
Fälle hat seinerzeit viel variiert, aber vom Ende des neunten Jahr-
zehntes im vorigen Jahrhundert ab beginnt ein stetiger Rückgang
der Malaria in Schweden, um vom Anfang dieses Jahrhunderts
völlig als endemische Krankheit zu verschwinden. Die finnische
Kurve zeigt, dass der Rückgang der Malaria ein wenig später
stattgefunden hat. Wir haben noch im Jahre 1902 über 3,300
Fälle gesehen und in den Jahren 1920—21 eine kleinere Endemie
mit etwa je 500 jährlichen Fällen erlebt.

Finnland gehört zu den Ländern, in denen Malaria zurzeit
verschwunden ist, obwohl der Anopheles dort noch überall vor-

handen ist. Der einzige in Finnland gefundene Anopheles ist der A. maculipennis,[1] dessen Verbreitung sich von Norden bis Süden und von Westen bis Osten über das ganze Land erstreckt. (Frey 1921). Meines Wissens ist in Finnland nie eine Malaria-Prophylaxie getrieben worden, weder in Form von prophylaktischer Chininabreichung noch in Form von Bekämpfung der Larvenentwicklung. Wasser und Möglichkeiten für Eiablage der Mücken gibt es noch immer genug im Lande. Auch kann nicht behauptet werden, dass eine wesentliche Klimaveränderung im Norden stattgefunden hätte. Während der letzten 100 Jahre hat sich das Klima höchstens in der Richtung verschoben, dass es mehr einen maritimen Charakter bekommen hat (Ångström 1939). Die Hypothese, dass die Malariamücken im Laufe der Zeit auf Grund eines vermehrten Viehbestandes zoofiler geworden seien, kann auch nicht in Finnland hervorgehoben werden, weil bei uns kaum eine relative Vermehrung des Viehbestandes stattgefunden hat. Die von Pihkala ausgerechnete Tabelle zeigt, wie sich der Viehbestand bei uns im Laufe der Zeit geändert hat:

Anzahl der Tiere pro hundert Leute der Landbevölkerung.

	Die über den Winter gehaltenen Tiere		Der Tierbestand am. 1. IX. 1939[2]
	1865	1900	
Pferde	15	13	10
Rinder	55	60	64
Schafe	53	42	33
Schweine	13	9	17

Die landschaftliche Verbreitung der Malaria war früher eine andere als jetzt. Erstens kam sie in Finnland auch nördlicher vorgekommen, und zweitens hat das Maximum der Fälle deutlich in den südwestlichen Teilen des Landes gelegen. Näheres siehe bei Sievers. Die Gruppierung der Fälle in den verschiedenen Teilen des Landes (17,575) während der Jahre 1892 bis 1. IX. 1943 ist aus meiner folgenden Tabelle zu erlesen.

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[1] Nach Ekblom (1938) kommen hier wenigstens die Formen typicus und messae vor.

[2] Die Zahlen aus d. J. 1939 sind nicht exakt mit denen aus dem Jahre 1865 und 1900 vergleichbar, aber der Fehler soll schätzungsweise (Pihkala). nicht 10 % überschreiten.

Die Verteilung von Malariafällen (17,575) zwischen den verschiedenen Provinzen während der Jahre 1892 bis 1. IX. 1943.

Uudenmaanlääni	35.2 %
Turun- und Porinlääni	48.7 %
Hämeenlääni	2.6%
Mikkelinlääni	2.2 %
Kuopion lääni	2.0%
Viipurinlääni	6.8 %
Vaasan lääni	1.1 %
Oulun lääni	1.4 %

Wie ersichtlich entstammen über 90 % der Fälle aus den drei südlichsten Provinzen: Uudenmaan-, Turun- und Porin- und Viipurinlääni.

Ich habe das obige Material nach drei Zeitperioden gruppiert, um dem Verschwinden der Malaria örtlich folgen zu können.

Die 17,575 Malariafälle nach Provinzen und nach drei Zeitperioden gruppiert.

	1892—1911		1912—1927		1928—1. 9. 43	
Uudenmaanlääni	4839	31.4%	1289	70.1%	51	16.0%
Turun- und Porinlääni	8350	54.1%	184	10.1%	25	7.9%
Viipurinlääni..........	943	6.1%	99	5.4%	153	48.1%
Die übrigen Provinzen zusammen	1302	8.4%	251	13.8%	89	28.0%
	15434		1823		318	

Die absolute Anzahl der Fälle in jeder Provinz ist fast ausnahmslos immer geringer geworden. Aber dadurch, dass das Verschwinden der Malaria schneller im Westen in der Provinz Turun- und Porinlääni stattgefunden hat als in den östlicheren Provinzen Uudenmaanlääni und Viipurinlääni, steigt die prozentuelle Anzahl der Fälle in Uudenmaanlääni in den Jahren 1912—1927 bis zu 70 %. Analoger Art sind die meisten Fälle in der allerletzten Zeit aus der östlichsten Provinz Viipurinlääni gemeldet worden.

Erst verschwindet also die Malaria aus Schweden und dann aus den südwestlichen Gebieten Finnlands, um zuletzt aus unseren östlichsten (und doch zugleich bedeutend kälteren!) Provinzen zu verschwinden. In Ostkarelien (Aunus) gibt es noch bedeutend

Malaria, worüber Pensala[1] berichten wird. In diesen Tat-
verhältnissen findet meines Erachtens die Hypothese von der
Einwirkung der sozialen Verhältnisse für das Verschwinden der
Malaria eine beachtenswerte Stütze, weil der Wohlstand der Land-
bevölkerung und die Hygiene der Ställe immer anspruchsloser
werden, je mehr wir nach Osten kommen.

Kurven, die das monatliche Vorkommen der Malaria in Finnland und in
Schweden angeben.
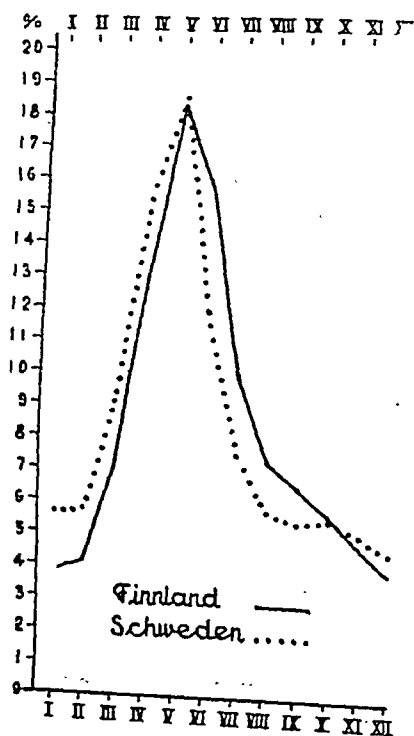
Kurve 2.

Das jahreszeitliche Vorkommen der Malaria in Schweden und
n Finnland lässt sich aus der Kurve 2 ersehen. In denen sind
lie sämtlichen Malariafälle (128,965)[2] Schwedens aus d. J. 1861—
940 aus den offiziellen Rapporten der Medizinalverwaltung mit-
genommen worden.

Das finnische Material umfasst 20,700 Fälle. Diese Summe

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[1] Er soll auch uber die in der Armée vorgekommenen Fälle berichten,
Diese gehen in meine Zahlen nicht ein.
[2] Aus dem ganzen Material 128,972 sind 7 Fälle weggelassen worden,
von denen die Angaben über das monatliche Vorkommen fehlen.

enthält erstens 2,002 Fälle, die von der Medizinalverwaltung in d
Jahren 1915—42 monatlich aus dem ganzen Land rapporti
worden sind, und dann auch 7,100 Fälle aus Helsinki in den Jahr
1881—1914, die von dem städtischen Gesundheitsamt gemel
worden sind, und drittens noch entsprechende 11,598 Fälle ɛ
Turku, die in den Jahren 1886—1914 amtlich gemeldet word
sind.
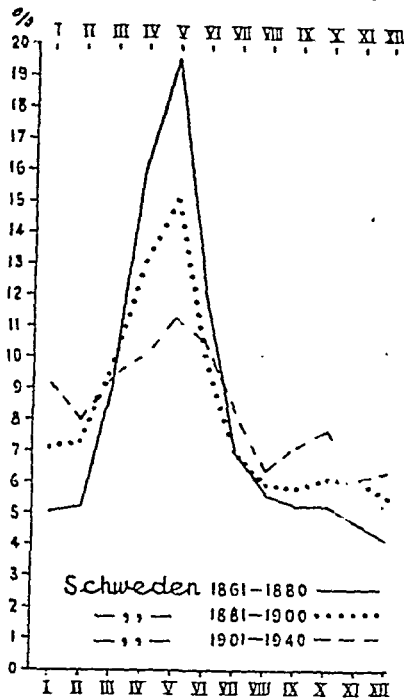
Kurv 3.

Wie ersichtlich fallen die Gipfel beider Kurven im Monat Mai
zusammen. Die Malaria in diesen nördlichen Ländern ist offenbar
eine Frühlings- und Frühsommer-Malaria gewesen. Allem Anschein
nach scheint die schwedische Malariawelle doch ein paar Wochen
früher zu steigen und auch früher abzuklingen als die finnische.
Rechnet man, wann die Fälle der Periode Februar-August im Mit-
tel vorgekommen sind bekommt man den Schwerpunkt[1] dieser

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[1] Die Summe: 1 mal die Fälle des Monats Februar plus 2 mal die des Mo-
nats März plus 3 mal die des Monats April plus 4 mal die des Monats Mai
plus 5 mal die des Monats Juni plus 6 mal die des Monats Juli plus 7 mal die
des Monats August dividiert durch die ganze Anzahl der Fälle während
Februar—August.

Epidemiewelle für den 24. Mai für Finnland und für den 13. Mai für Schweden. Man könnte behaupten, dass diese Verschiedenheit dadurch bedingt wäre, dass die schwedische Kurve wesentlich von der Malaria der Jahre 1861—80 abhängig sei, die vielleicht früher manifest wurde als die der Jahre 1881—1940. In der Darstellung, Seite 266 habe ich das schwedische Material diesem Gesichtspunkt nach gespalten, und die monatlichen Kurven aus den Jahren 1861—80 (97,109 Fälle), 1881—1900 (30,095 Fälle) und 1901—1940 (1,761 Fälle) getrennt gezeichnet.

Wie ersichtlich hat im Gegensatz zu der im Laufe der Zeit entstandenen tiefen Veränderungen der Malariakurve in Holland (Swellengrebel) keine Verschiebung der Malariawelle in Schweden stattgefunden. Werden die Schwerpunkte für alle drei Kurven berechnet, bekommt man das Mittel für die Jahre 1861—80 auf den 14. Mai, für die Jahre 1881—1900 auf den 10. Mai, und für die Jahre 1901—40 auf den 13. Mai. Die Differenz zwischen Finnland und Schweden scheint real zu sein. Die Malaria in Schweden hat aber im Laufe der Zeit ihren epidemischen Charakter derart verändert, dass die Epidemiewelle in Schweden nicht mehr so steil wie früher steigt. (Kurve 3).

Der Vergleich der beiden Kurven Finnland-Schweden (Kurve 2) ergab eine gewisse Verspätung der finnischen Malaria in Bezug auf die schwedische. Ich habe diesen Unterschied besonders hervorgehoben, erstens weil als eine allgemeine Tatsache hervorgehoben wird, dass je nördlicher um so früher die Malariaepidemien anzufangen scheinen. Zweitens wird diese Tatsache interessant dadurch, dass sie die alte Hypothese von Robert Koch zu stützen scheint. Er vermutete ja bekanntlich, dass die überwinternden Mücken die nördliche Malariawelle verursachten. Hierbei scheint der Parallelismus je früher die Mücken fliegen um so früher steigt die Malariawelle verlockend. Die entgegengesetzte und nunmehr allgemeiner anerkannte Hypothese, die z. B. von Ruge und Kikuth verfochten wird nimmt an, dass die Frühlingswelle durch eine Infektion im Herbst nach einer langen Inkubationszeit erst im folgenden Frühjahr ausbricht. In Finnland und Schweden haben wir aber zwei Länder, deren Malariaepidemien innerhalb weiter Grenzen vergleichbar sind. In Finnland, wo der Herbst früher kommt und der Frühling später eintritt, hätten wir also eine längere Inkubationszeit als in Schweden. Warum? Diese Tat-

sache scheint mir in gewissem Masse für die Hypothese Kochs
zu sprechen.

Um die Frage zu beleuchten habe ich das finnische Material
gespaltet und separat einerseits die monatlichen Verteilungs-
kurven für Turku und die südwestlichsten Teile des Landes (11,78
Fälle aus d. J. 1886—1942) und andererseits die übrigen finnischen
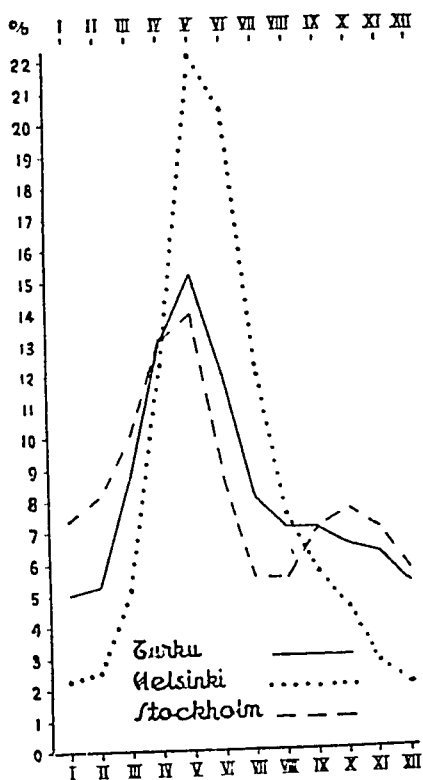
Kurve 4.

Fälle (8,916 aus d. J. 1881—1942) gezeichnet, die also meistens
aus Helsinki entstammen. Zum Vergleich sind hier noch als eine
dritte Kurve die 3,369 Fälle von Stockholm und Umgebung (aus
d. J. 1887—1919) gezeichnet. Beim Vergleich dieser drei Kurven
bemerkt man, dass die Kurve von Stockholm früher steigt als die
von Turku, und diese wieder früher als die von Helsinki. In
derselben Ordnung klingen die Kurven wieder ab. Unter diesen
nicht weit voneinander liegenden Städten scheint also die Früh-
lingswelle um so früher zu steigen je grösser das Jahresmittel

m Ort und Stelle ist. Werden ·die Schwerpunkte der Kurven für
lie Periode Februar—August ausgerechnet, findet man sie für
Stockholm am 5. V., für Turku am 17. V. und für Helsinki
am 30. V. Die Mitteltemperaturen der betreffenden Orte betragen:
n Helsinki 4.4°, in Turku 4.6° und in Stockholm 5.9°. Die Tempe-
raturdifferenzen zwischen Helsinki und Turku sind nicht gross,
aber dabei sind wir auch ganz an die nördlichste Grenze der Ma-
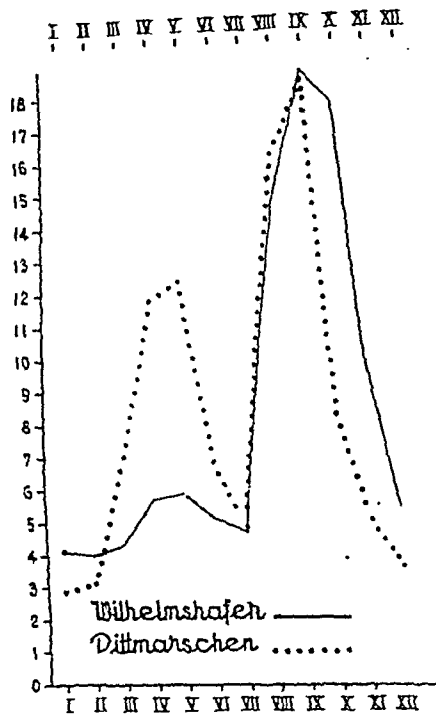
Kurve 5.

lariaverbreitung gekommen, und hier könnte sich sogar eine kleine
Differenz bemerkbar machen.

Je weiter man von Stockholm nach Süden kommt, um so
früher könnte man die Frühlingswelle erwarten. Das ist aber nicht
der Fall. In Kalmar liegt der Gipfel der Frühlingswelle in den Mo-
naten April—Mai, der Schwerpunkt am 9. Mai, ähnlich wie im
Dittmarschen (Schwerpunkt am 10. Mai nach Dose) und in
Wilhelmshafen (Schwerpunkt am 16. Mai nach Wenzel) oder früher
in Holland nach Swellengrebel (Schwerpunkt etwa am 13. V.).

Vergleicht man die Kurven im übrigen so ist zu notieren, wie
die nordischen Kurven monophasisch sind. In Stockholm und in

Kalmar lässt sich eine Herbstwelle ahnen, und schon vom Di
marschen an hat sie sogar über die Frühlingswelle domini

Die zwei phasischen Kurven aus dem Dittmarschen, Wilheh
hafen und aus Holland sind aber alte Kurven. Die jetzige Ku
Hollands ist nach Swellengrebel monophasisch. Es ist möglich, c
auch in Finnland in älteren Zeiten die Malariakurve einen klei
Herbstgipfel gehabt hat. Bei uns ist aber immer, soweit wir wiss
die Frühlingsmalaria die Hauptsache gewesen. Im Herbst gal
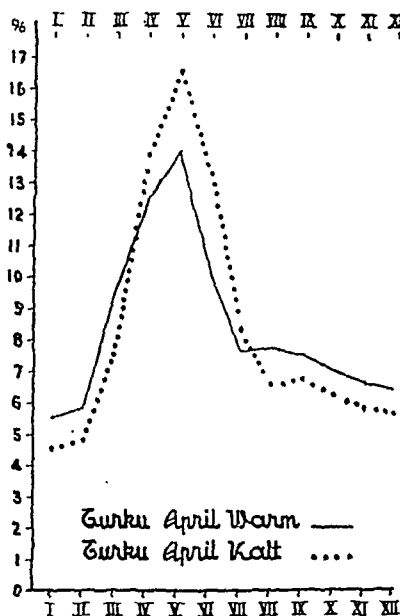
Kurve 6.

früher eine quartana autumnalis, die zum letzten Male aus dem
Jahre 1861 erwähnt wird. (Sievers). Laut seinen Zusammenstel-
lungen wird sie zum ersten Male aus dem Distrikt Pori aus dem
Jahre 1767 erwähnt, dann ist sie aus den Jahren 1818, —19, —20,
—27, —28, —30, —31, —32, —34, —44, —46, —47, —48, —49,
—53, —55, —56 beobachtet worden, zwar 14 mal ausdrücklich aus
dem Herbst (Oktober), 2 Mal im Frühling. Aber auch die Tertiana
wird dann und wann im Herbst wieder an Zahl zunehmen, z. B.
in d. J. 1750, 1757, 1832, 1846, 1847 und 1861. Es scheint, als
ob die Tertiana-Fälle ein wenig früher im Herbst zum Ausbruch
kämen als die quartana. (vgl. Stigzelius a. J. 1819—20).

Um noch die Mückentheorie zu prüfen und um zu sehen welchen Einfluss die warmen und kalten April-Monate für das Vorkommen der Malaria haben, habe ich das obige Material aus Turku gespalten, sodass ich einerseits die Malariakurve (5,290 Fälle)
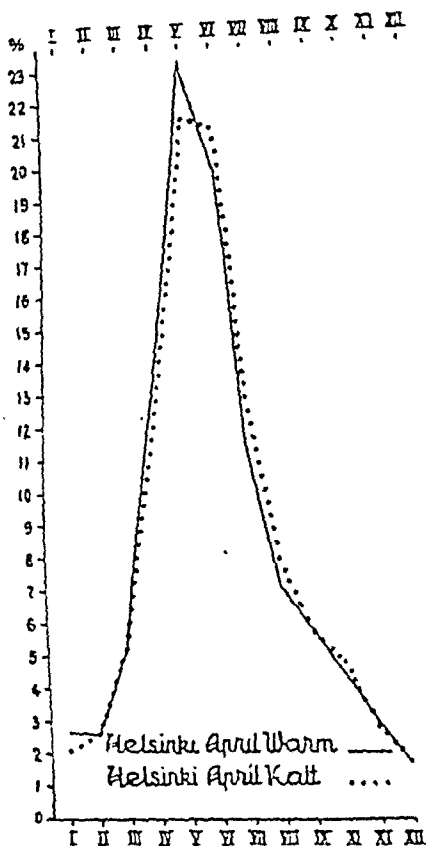
Kurve 7.

aus den 30 Jahren gezeichnet habe, die im April die wärmsten waren, d. h. eine Temperatur plus 2.5° Grad oder mehr betrugen[1] und andererseits die Kurve (6,494 Fälle) der 27 kälteren Apriljahre. Wie ersichtlich (Kurve 6) liegt die Welle mehr nach links, wenn der April warm ist, d. h. sie tritt dann früher auf, als wenn dieser kälter ist. Die Schwerpunkte liegen zwar nicht weit voneinander am 16. bezw. am 19. Mai, falls die Periode Februar—August

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[1] Die Temperaturgrenze ist hierbei wie auch im Folgenden so gezogen, dass eine möglichst gleiche Anzahl der Jahre auf beiden Seiten der Grenze fällt. Für die Temperatur-Angaben, die ich von Professor Keränen für Finnland und von Direktor Slettenmark für Stockholm bekommen habe, danke ich verbindlichst.

berücksichtigt wird.   Die Differenz ist tatsächlich 3 Tage grösser,
wenn der Monat August weggelassen wird, was mathematisch richtiger ist, weil der Monat Juli einen kritischen Wendepunkt zeigt.

Analoger Art habe ich das Material von Helsinki nach der
Temperatur im April gespaltet (Kurve 7).   Dabei ist plus 2 Grad
als die Grenze betrachtet. Die Jahre, die plus 2° oder mehr im
Mittel gewesen sind, sind als warme betrachtet. Dabei kommen auf
die warmen 32 Apriljahre 3,837 Fälle, und auf die kalten 30 Jahre
5,070 Malariafälle.

Der Unterschied zwischen den warmen und kalten Apriljahren
ist also kaum bemerkbar, obwohl er von gleicher Art ist wie in
Turku.   Die Differenz des Schwerpunktes am 29. und 31. Mai
beträgt nur 2 Tage.

Wird das gesamte Material aus Schweden (128,965 Fälle) nach
denselben Prinzipien gespaltet, und wird die Grenze der warmen
und kalten Jahre auf Grund der Apriltemperatur in Stockholm
bei 3° gezogen, dann fallen die Schwerpunkte der warmen und kalten Jahre auf denselben 13. Mai zusammen. Ein Unterschied, wie
wir es in Turku gesehen haben, lässt sich hier nicht wiederfinden.

Die von uns gestellte Arbeitshypothese, die die Differenzen in den
Malariakurven Schwedens und Finnlands zu erklären sucht, kann
also verallgemeinert nicht aufrecht erhalten werden.

Bei der Analyse der warmen und kalten Apriljahre fiel es uns
auf, dass die kalten Jahre mehr Malaria aufzuzeigen schienen als
die warmen. In die folgende Tabelle nehme ich die Zahlen aus
Helsinki, Turku und Schweden.

	Kalte Apriljahre				Warme Apriljahre				
	Anzahl d. Jahre	April-temp.	Malaria fälle insges.	Malaria fälle p. Jahr	Anzahl d. Jahre	April-temp.	Malaria fälle insges.	Malaria fälle p. Jahr	D. Unterschied der Warmen Jahre von der kalten in %
Helsinki 1881—1942	30	1.9 u. weniger	5070	*189*	32	2.0 u. mehr	3837	*120*	—36.0
Turku 1886—1942	27	2.4 » »	6494	*241*	30	2.5 » »	5290	*178*	—26.0
Schweden 1861—1940	38	3.5 » »	78008	*1947*	42	3.6 » »	52957	*1306*	—33.8

Wie ersichtlich sind an allen drei Orten während der wärmeren Apriljahre etwa 25—35 % weniger Malariafälle vorgekommen als während der kälteren Jahre. Somit scheint also ein kalter April-Monat mehr Malaria mit sich zu bringen als ein warmer.

Es liegen Beobachtungen aus Dänemark (Hansen 1886) und aus Finnland (Sivén 1904) vor, dass je wärmer der vorausgegangene Sommer gewesen ist, um so mehr ist im folgenden Jahr Malaria gefunden worden. Die grossen Zahlen aus Schweden scheinen dies nicht ganz zu bestätigen. Falls die 38 Julimonate in Betracht gezogen werden, die in Stockholm 16.8° oder mehr gezeigt haben, dann kommen auf diese folgenden Jahre nur 61,162 Fälle von Malaria, d. h. 1,610 Fälle pro Jahr. Die 42 Jahre, deren vorausgegangener Juli kälter war, zeigen 67,803 Fälle, d. h. 1,614 Fälle pro Jahr. Wird aber die entsprechende Grenze bei 16.7° gezogen, dann zeigen die 43 »warmen» Jahre 75,149 Fälle, und die »kalten 53,816 Fälle, pro Jahr also 1,748 bezw. also 1,460 Fälle. Der Unterschied wäre dann also + 16.5 %. Verglichen mit dem Einfluss der Apriltemperatur scheint die Juliwärme des vorausgegangenen Jahres von geringerem Einfluss zu sein.

Zum Vergleich habe ich noch den Einfluss der September-temperatur des vorausgegangenen Jahres ausgerechnet:

	Septemb. des vorausgegangenen Jahres kalt				bezw. warm				D. Unterschied in %
	Anz. d. Jahre	September-Temp. d. vorausgegangenen Jahres	Anzahl d. Fälle	Fälle p. Jahr	Anz. d. Jahre	September-temp. d. vorausgegangenen Jahres	Anz. d. Fälle	Fälle d. Jahr	
Helsinki 1881—1942	31	10.8 u. weniger	3048	98	31	10.9 u. mehr	5868	170	+73.5
Turku 1886—1942	28	10.5 » »	5697	204	27	10.0 » »	6088	225	+10.3
Schweden 1861—1940	41	11.2 » »	69228	1688	39	11.3 » »	59737	1532	+ 9.2

Die Zahlen variieren stark, aber ähnlicherweise wie ein warmer Juli-Monat scheint auch ein warmer September-Monat mehr Malaria mit sich im folgender Jahre zu bringen.

Die ausgeführte statistische Analyse zeigt also, dass vielleicht

die Apriltemperatur von gewissem Einfluss für das Vorkommen
der Malaria ist. Da aber die Anzahl der grossen Malariajahre
auch im schwedischen Material doch klein bleibt, habe ich
diese Behauptung näher prüfen wollen. Deshalb habe ich die
Fälle von Schweden in zwei willkürliche Gruppen gespaltet und
zwar nach der Temperatur im vorausgegangenen September
und getrennt in beiden diesen Gruppen die Wirkung der April-
temperatur berechnet. (Die Temperaturgrenzen sind dieselben wie
in den obigen Tabellen):

	Anz. d. Jahre	Anz. d. Fälle	Anzahl der Fälle pro Jahr
Schweden: September kalt u. April kalt	20	37,511	1,876
» » u. » warm	21	31,717	1,510
» warm u. » kalt	18	38,497	2,139
» » u. » warm	21	21,240	1,011

Die Wirkung eines kalten Aprilmonats macht sich also in den
beiden Gruppen geltend.

Ich habe noch getrennt die Jahre 1861—91 analysiert. In
diese Zeitperiode gehen nämlich nur solche Jahre ein, die über
1,000 Fälle zeigen. Diese Nachprüfung ist besonders auch dadurch
zu motivieren, weil die Temperatur damals ein wenig kälter als
in diesem Jahrhundert gewesen ist. Die Grenze der kalten und
warmen Aprilmonate muss hier bei einer 0.6 Grad kälteren Stelle
gezogen werden als in der Tabelle S. 272.

	Anzahl d. Jahre	Anz. d. Fälle	Anzahl d. Fälle pro Jahr
Schweden: April kalt, + 2.9 oder weniger	15	67,278	4,485
» warm, + 3.0 » mehr	16	54,588	3,412

Wie man es auch berechnen mag, immer zeigt sich die malaria-
befördernde Wirkung des kalten Frühlings. Wie ist das zu erklären?
Nimmt man eine lange Inkubationszeit an, so lässt sich das
nicht ohne weiteres verstehen. Man muss irgendwelche Hilfshypo-
thesen annehmen oder die ganze Beobachtung verneinen. Nimmt

man aber an, dass die Frühlingsfälle zum grossen Teil Neuinfektionen seien, wird die Erscheinung verständlicher, wenn man nur bedenkt, dass während des kalten Frühlings das Zusammenleben der Menschen und Tiere zwangsweise ein längeres ist, und dass während dieser Zeit die Menschen mehr in den Malariahäusern und Malariaställen der Infektion ausgesetzt sein müssen.

Zusammenfassung.

Es werden statistische Angaben über die Malaria in Finnland angegeben. Die monatliche Verteilungskurve zeigt, dass in Finnland die Malaria ein wenig später als in Schweden auftritt. Ein kalter Frühling scheint mehr Malariafälle im Norden zu prädisponieren als der wärmere. Auf die Schwierigkeit diese Beobachtung mit der Theorie von langer Inkubationszeit zu erklären wird hingewiesen. Das stufenweise Verschwinden der Malaria aus den verschiedenen Teilen Finnlands wird mit dem Wohlstand und der Kultur der Provinzen verglichen.

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Influence des Variations de l'Imprégnation oestrinique sur le Métabolisme basal et l'Activité thyroidienne.

Etude expérimentale et clinique.

Par

JACQUES MAHAUX.

(Ce travail est parvenu à la rédaction le 28 Avril 1944).

Dans son traité du goitre, en 1850, Coindet remarque combien «les causes physiologiques d'hypertrophie thyroidienne agissent plus particulièrement sur le sexe féminin. Elles paraissent dues à la sympathie qui existe entre le cou et le système reproducteur. C'est ainsi que le goitre commence le plus souvent avec la première grossesse et devient plus volumineux après chacune d'elles. Il en est de même pour l'allaitement. Dans un grand nombre de cas, il se développe aux approches de l'âge critique. Ces diverses causes expliquent pourquoi, dans l'âge adulte, le goitre est beaucoup plus fréquent chez les femmes que chez l'homme.»

Ces relations évidentes de la fonction ovarienne et de l'activité thyroidienne ont suscité de nombreuses recherches expérimentales. Divers auteurs ont étudié l'action des corps oestrogènes sur le métabolisme basal.

Action des corps oestrogènes sur le métabolisme basal et la sensibilité à la thyroxine.

Laqueur, Hart et De Jongh ont signalé, en 1926, que l'oestrine augmente de 15 à 20 % le métabolisme basal de rats normaux ou ovariectomisés. v. Arvay (1931) note une intensification des

combustion du même ordre de grandeur pendant l'oestrus provoqué par l'injection de 1,000 u.i. d'oestrine, durant 10 à 16 jours, à des rats femelles castrés ou non.

De nombreuses recherches ultérieures sont en opposition complète avec ces premiers résultats. Kunde, D'Amour, Carlson et Gustavson (1930) constatent que le métabolisme basal de chiennes adultes montre un très léger abaissement lors de l'administration continue d'oestrine entrainant le rut.

Sherwood, Savage et Hall (1933) mesurent une chute constante du métabolisme basal, variant de 13 à 42 %, chez des rats et des lapins injectés de 10 à 800 u.r. de corps oestrogènes (amniotine). Chez un lapin, dont les combustions étaient maintenues élevées par de l'extrait thyroïdien, l'oestrine fait tomber celles ci à —8 %. L'hormone ovarienne produit encore une diminution du métabolisme basal chez le rat adulte ovariectomisé, celle ci peut être suivie d'une légère élévation au dessus de la normale, vraisemblablement par surcompensation. L'injection d'oestrine à des animaux à métabolisme augmenté par la thyroide entraine un retour à la normale une fois et demie plus rapide que chez les témoins (Sherwood et Bowers — 1936). Chez le rat thyroidectomisé, l'oestrine ne modifie pas les combustions (Sherwood, Wilson et Bonete — 1937). Cette administration d'oestrine réduit de 24 à 12 jours la durée de la période d'hypermétabolisme qui suit l'administration d'une dose déterminée d'extrait thyroidien (Sherwood — 1938) (1).

Gessler (1936—1937) constate que des cobayes traités par de l'extrait thyroidien, puis injectés d'oestrine (5,000 u), présentent un métabolisme basal moins élevé (+ 22.3 %) que les témoins (+ 37.9 %). Lors de l'administration simultanée de thyreostimuline et d'oestrine (1,000 u. par jour), 7 animaux sur 13 ne montrent pas d'élévation de leurs combustions; chez les autres, le métabolisme augmente soit normalement, soit dans des proportions moindres que chez les témoins.

Danforth, Greene et Ivy (1937) constatent que les rats injectés d'oestrone, d'oestriol, d'emménine (facteur oestrogène du placenta) et de progestérone et traités par de la thyroide montrent une moindre élévation de métabolisme que les témoins ne recevant pas d'hormones sexuelles.

Grumbrecht et Loeser (1938) signalent que l'injection de grosses doses d'oestradiol diminue le métabolisme basal de rats femelles.

Collet, Smith et Wertemberger (1937), au cours de périodes d'observation étendues, on fait une étude remarquable de l'action des corps oestrogènes sur le métabolisme basal de la femme ovariectomisée. Ces patientes présentent un métabolisme basal variant de —12 à —20 %, beaucoup plus stable que celui de la femme normale. L'injection de doses importantes d'oestrine entraine en général une chute des combustions pendant la période de médication; il se produit une élévation compensatoire dans les semaines qui suivent. On note la réapparition de fluctuations journalières de grande amplitude.

Frappé par la discordance des résultats expérimentaux des premiers auteurs cités, nous avons, de 1937 à 1944, repris l'étude de l'action de l'oestrine sur les combustions basales en nous plaçant dans les conditions expérimentales les plus rigoureuses possible. Nous avons rejetté l'emploi du cobaye, animal nerveux, agité et donnant facilement des valeurs de combustions trop élevées, pour adopter le lapin qui fournit des taux de métabolisme basal très stables. Les mesures, d'une durée moyenne de deux heures, ont été effectuées au moyen de l'appareil de Knipping, elles ont lieu tous les deux jours. Les sujets sont mis à jeun une vingtaine d'heures avant la mesure, ils sont entrainés aux déterminations de métabolisme et aux injections (sérum physiologique) pendant une période de 15 jours au moins avant d'être l'objet d'expérimentations.

Dans ces conditions, on constate que l'administration journalière de 6,000 à 25,000 u.i. benzoïques de benzoate d'oestradiol à des lapins femelles (ou mâles), pesant 2 à 3 kg entraine régulièrement, endéans 24 à 72 heures, une chute nette de leur métabolisme basal. Celui ci se fixe d'emblée à des valeurs de l'ordre de —10 à — 40 %. Après arrèt des injections, il se produit un relèvement progressif à la normale et même au delà. L'emploi de dipropionate de diéthyldioxystilbène provoque des modifications des combustions superposables.

Des sujets soumis à un traitement chronique (2 à 4 mois) par des doses moyennes d'oestrine montrent, après une dépression initiale prolongée, une tendance au relèvement de leur métabolisme. L'examen de ces animaux révèle une augmentation nette du poids de leur thyroide.

Nous avons obtenu des résultats analogues par greffes sous cutanées de comprimés d'hormones sexuelles. Des circonstances
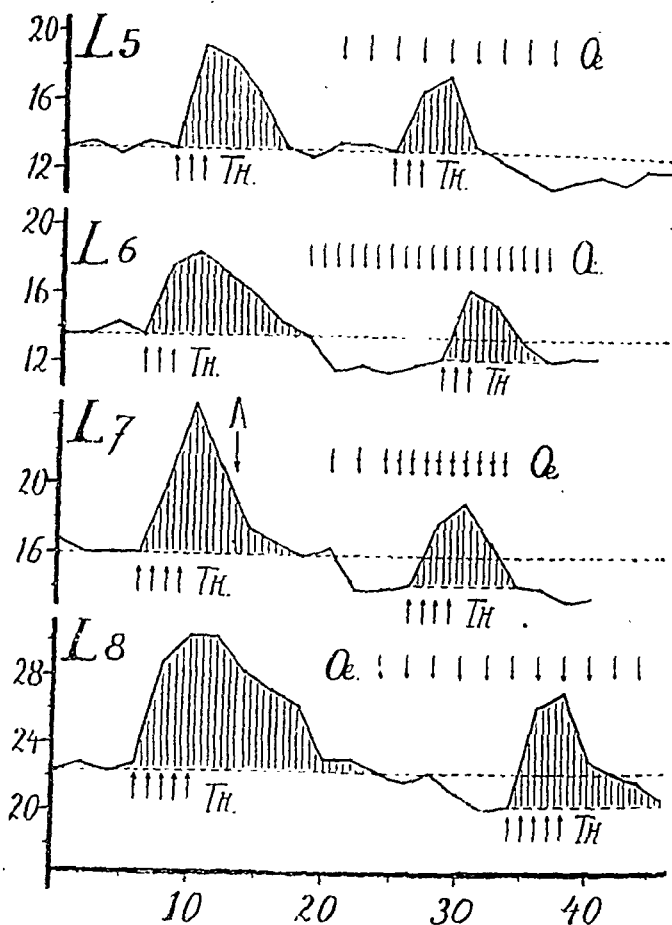
Fig. 1. — En abscisse, le temps. En ordonnée, consommation d'oxygène en décilitre/heure. TH.: chaque flèche = 1 mg de thyroxine. — Oe.: flèches simples = 12,500 u.i. benz. oestradiol en sol. huileuse. — Flèches doubles = 25,000 u.

L'administration de benzoate d'oestradiol a pour effet immédiat une dépression notable du métabolisme basal. On constate une diminution nette de l'action calorigène de la dose de thyroxine injectée. Des expériences témoins montrent que chez le lapin adulte, non traité par l'oestradiol, la même dose de thyroxine garde une valeur calorigène très constante au cours d'une période assez étendue. (Mahaux. — C. R. Soc. Biol., CXXX, 77, 1939.)

imprévues nous ont malheureusement interdit d'étudier la structure thyroïdienne des animaux implantés depuis un temps assez long, ainsi que les modifications des combustions survenant lors de l'épuisement du greffon hormonal.

Chez des lapins maintenus en état d'hypermétabolisme constant, prolongé, par administration journalière de thyroxine, des

injections d'oestrine (30,000 à 100,000 U.) permettent d'obtenir une dépression prolongée des combustions.

Afin de préciser le mécanisme de cette chute du métabolisme, nous avons exploré systématiquement la sensibilité à la thyroxine du lapin avant et pendant l'imprégnation oestrinique. On constate régulièrement une diminution nette et parfois considérable de l'action calorigène de la thyroxine ou des extraits thyroidiens (Elityran) utilisés (Fig. I). La perte de poids déterminée par une quantité déterminée de thyroxine est toujours moindre au cours de la période de traitement par l'oestrine (2).

En résumé: Si l'on excepte les deux premiers travaux, dont les résultats aberrants résultent probablement plutôt de l'augmentation de l'activité motrice des animaux en rut que d'une hausse vraie de leur métabolisme basal, les constatations des nombreux auteurs qui ont étudié l'action des corps oestrogènes sur les combustions sont concordantes.

L'établissement d'une imprégnation de l'organisme par des doses élevées de corps oestrogènes entraine une chute rapide du métabolisme basal. L'action calorigène de la thyroxine est diminuée dans son intensité et dans sa durée. Il s'est créé un état de thyroxinorésistance oestrinique ou polyoestrinique.

Un traitement oestrinique prolongé, ou discontinu, permet cependant de noter un relèvement des combustions à la normale ou au dessus de celle-ci, qui parait résulter d'une augmentation compensatrice de l'activité thyroidienne.

Remarquons que l'ablation totale de la thyroide n'entraine qu'une chute très progressive des combustions, lesquelles n'atteignent leur niveau le plus bas qu'après deux ou trois semaines et plus. La dépression oestrinique du métabolisme, par contre, s'établit brutalement, en 2 ou 3 jours. Il est donc peu justifié de l'attribuer à un freinage de l'activité thyroidienne. D'ailleurs, la diminution du pouvoir calorigène d'une quantité déterminée de thyroxine exogène indique que l'action de l'oestrine doit se produire au niveau du point d'attaque de la thyroxine sur les combustions.

Dans ces conditions, on voit que, toutes choses égales d'ailleurs, l'établissement d'une imprégnation oestrinique chez un homeotherme, ou son augmentation, doit entrainer régulièrement une chute de son métabolisme basal. A activité thyroidienne constante, les périodes d'oestrinémie élevée de la vie féminine: puberté,

grossesse, phase polyoestrinique de la ménopause devraient s'accompagner d'une réduction des combustions. Le sujet normal ne montre rien de pareil. Le métabolisme basal est plutôt en voie d'accroissement lors de la période prépubertaire et pubertaire, il *montre une légère élévation à la fin de la grossesse et varie peu à la* ménopause. Mais c'est précisément au cours de ces périodes qu'on constate souvent une hypertrophie de la thyroïde pouvant aboutir à la formation d'un goitre parenchymateux, parfois volumineux. L'absence de dépression des combustions résulte de l'action compensatrice d'une augmentation de l'activité thyroïdienne.

Prépuberté, Puberté et Début de la Vie féminine.

>Tranquillise toi, mon enfant, Vénus t'a touché de la main et
t'avertit doucement que ton petit corps va se transformer.>
Goethe, à propos d'un goitre prépubéral.

>Non illam nutrix orienti luce revisens
Hesterno collum poterit circumdare filo>.
Catulle.

La puberté féminine entraine régulièrement une activation de la thyroïde qui se manifeste souvent par une hyperplasie de la glande. Le *rôle de développement génital dans le déterminisme* de cette réaction glandulaire est connu depuis longtemps, à tel point que, dans certaines régions goitrigènes, la tradition locale voulait que les jeunes filles dépourvues de goitre soient impropres au mariage.

Engelhorn, ainsi que Seitz, en 1912, attribuent l'apparition de cette hypertrophie thyroïdienne à l'inondation de l'organisme par la sécrétion interne de l'ovaire. Aschner observe une hyperplasie de la thyroïde chez des jeunes femmes traitées par des injections d'oestrine dans l'espoir de corriger une hypoplasie mammaire. Engelhorn note un développement constant de la thyroïde chez les animaux en période d'oestrus. I. Leitch (1927) constate une élévation de l'iodémie au même moment.

Watrin et Florentin (1928) observent une forte activation de la thyroïde chez le cobaye injecté de liqueur folliculaire de vache. .L'administration de corps oestrogènes, extrait ovarien ou composés synthétiques, entraine souvent une hyperplasie thyroïdienne chez l'animal (Kunde, D'Amour, Gustavson et Carlson — 1930,

Pincus et Werthessen — 1933, W. Hartogh — 1933, Sturm et Schönig — 1935, Amilibia et Mendizabal — 1936, etc).[1] Selon Loeser (1938), tout accroissement de la sécrétion de corps oestrogènes détermine une activation thyroidienne, qui nécessiterait toutefois la présence d'un relai utérin.

Cette augmentation juvénile de l'activité thyroidienne, venant compenser l'action hypométabolique des corps oestrogènes, s'accompagne de signes assez particuliers. On constate souvent l'apparition d'un certain éclat du regard, qui fait partie du charme féminin, mais ne va pas sans rappeler les yeux brillants et même l'exophtalmie de la maladie de Basedow. Tout se passe comme si, comme dans cette affection, il existait une excitation simultanée d'un centre stimulant la thyroide et d'un centre exophtalmiant. Il n'y a cependant ni amaigrissement, ni transpiration exagérée. Le rythme cardiaque, en l'absence d'une tachycardie émotive fréquente, ne se montre pas accéléré. La mesure du métabolisme basal donne régulièrement des chiffres normaux.

Les observations de Kerley (1936) (3), chez des enfants dépourvus de thyroide, nous donnent des précisions numériques sur cette augmentation physiologique des besoins en sécrétion thyroidienne. Chez un des sujets étudiés, la quantité d'extrait nécessaire au maintien d'un état normal, qui était de 15 ctg à 5 ans et de 30 ctg à 10 ans, passe à 42 ctg après établissement des règles à 14 ans, puis à 54 ctg à 20 ans et à 72 ctg à 25 ans (cf. Fig. III).

La tolérance aux extraits thyroidiens des jeunes filles porteuses d'un goitre juvénile est souvent remarquable. Nous avons pu administrer d'une façon continue des doses de 30 ctg à 1 g sans provoquer la moindre manifestation d'hyperthyroidie.

Nous pensons que l'apparition chez une jeune fille d'une hyper-

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[1] Il faut noter, en opposition avec ces résultats, que des traitements oestriniques, généralement intensifs et prolongés, peuvent entrainer la mise au repos et même l'atrophie de la thyroide (Lundberg — 1927, Bisceglie — 1930, Bratiano et Farcki — 1932, Bialet — Laprida — 1933, Sigurt Franck, Karp et Kostiewitz — 1933, Heyl, De Jongh et Kooy — 1934, del Castillo et Sammartino — 1937.), probablement par blocage du système excitosécrètoire de la glande. Pour obtenir des effets superposables aux réactions physiologiques, il faut réaliser chez l'animal des conditions d'expérience comparables, toutes proportions gardées, à celles qui se produisent chez l'homme. La gradation de l'établissement d'une imprégnation oestrogène, ses limites physiologiques et pathologiques, la qualité des divers oestrogènes actifs, l'action d'une imprégnation hormonale antérieure ou concomitante, lutéinique ou autre, l'influence de la nature de l'animal et de son âge, sont autant de facteurs encore imparfaitement étudiés.

trophie thyroidienne notable, sans signes cliniques d'hyperthyroïdie, correspond pratiquement toujours à une élévation considérable de son imprégnation oestrinique, même s'il existe une aménorrhée ou une oligoménorrhée. Les troubles menstruels virginaux polyoest riniques sont malheureusement souvent méconnus et traités pa injection de doses parfois massives de corps oestrogènes, ce qui n peut qu'accentuer une hyperplasie thyroidienne débutante.

Obs. — B. Mina, 13 ans (1939). Pas de goitre dans la famille. 1ères règle à 10 ans, d'abord très irrégulières. A 12 ans, on constate l'existence d'un hypertrophie thyroidienne modérée. La jeune fille est traitée régulière ment par l'injection de doses élevées de benzoate d'oestradiol, «afin de fre ner la thyroide». Le résultat est décevant: les règles tendent à s'espace la thyroide prend un développement considérable.

On note, en 1939, la présence d'un gros goitre parenchymateux diffu occupant toute la largeur du cou. Il n'existe aucun signe cliniq ni d'hyper, ni d'hypothyroidie. M. B.: — 1 %, le 15 juillet 1939. C administre de l'extrait thyroidien (10, puis 20 et 30 ctg, 15 jours par moi afin de mettre la glande au repos par substitution. Après deux ans de traitement, le goitre a entièrement disparu, la thyroide est à peine aug mentée de volume. Le tour de cou a passé de 40 à 34 cm, alors que le poids de la patiente a augmenté de 57 à 64 kg. Les règles sont normales, régu lières.

Un métabolisme basal normal ou même légèrement abaissé chez un sujet goitreux ne doit pas nécessairement faire conclure à une thyroide inactive, de structure colloide. En présence d'une femme jeune, on doit penser plutôt à un état d'oestrinémie élevée où la thyroide, très active, s'hyperplasie afin de compenser l'action hypométabolique de la sécrétion ovarienne. Marañon reconnait un »accent féminoide» au corps thyroide. Il décrit le »bocio genital», hypertrophie plus ou moins marquée de la glande lors des périodes d'activité génitale de la femme.

Obs. — V. Jeanne, 28 ans. Envoyée avec le diagnostic de »goitre col loide» avec hypothyroidie. Antécédents nuls. Un enfant de 5 ans. La thyroide a fortement augmenté de volume depuis un an, elle atteint actuel lement la taille d'une orange. Sa consistance est homogène. Les régles sont régulières, très abondantes (28/9). Examen gynécologique négatif. M. B.: — 10 %, le 26 juin 1942. Il n'existe aucun signe d'hyperthyroidie. La malade est un peu frileuse, elle a tendance à grossir.

Un prélèvement thyroidien donne le résultat suivant: »Signes d'hyper plasie d'aspect basedowien, vésicules irrégulières, parfois papillifères, cel lules hautes» (Prof. Dustin). Nous ne possédons malheureusement pas de

biopsie de la muqueuse utérine, ni de dosage de corps oestrogènes dans le sang ou les urines de la malade, ce qui aurait pu démontrer fermement le diagnostic d'hyperoestrinémie.

Deux mois après, la patiente a encore grossi de 9 kg. M. B. — 12 %, le 5 novembre 1942. La thyroide est toujours volumineuse. On administre des doses appréciables d'extrait thyroidien afin de mettre la glande au repos.

Les cas de ce genre paraissent correspondre à une augmentation considérable des besoins en thyroxine, que la thyroide, malgré son hyperplasie, ne parvient pas toujours à satisfaire; il peut en résulter l'apparition de légers signes d'hypothyroidie. Henschen (1931) remarque que de tels sujets, porteurs d'un goitre sans signes cliniques d'hyperthyroidie, avec métabolisme basal normal ou inférieur à la normale, peuvent présenter une iodémie nettement élevée (35, 38, 45 gammas).

Cette élévation des besoins en sécrétion thyroidienne parait résulter de la thyroxinorésistance relative qu'entraîne une imprégnation oestrinique élevée, dont le laboratoire ne permet pas encore, à l'heure actuelle, de chiffrer aisément la valeur. Les procédés biologiques de dosage des corps oestrogènes sont d'application difficile. La mise au point d'un dosage chimique ou physicochimique constituerait certainement un progrès considérable.

Rappelons que Boothby et Plummer avaient déjà remarqué la thyroxinorésistance relative des »goitres colloides». Ils l'attribuent toutefois à une résorption intestinale imparfaite de la thyroxine qui serait propre à cette variété de goitre.

Le taux élevé des corps oestrogènes dans les fibromes et dans la fibromatose utérine détermine souvent le développement d'une hypertrophie thyroidienne. Aschner (1924) observe une augmentation de la thyroide dans 90 % des cas de fibrome. Réciproquement, l'utérus et les ovaires des femmes goitreuses sont fréquemment augmentés de volume.

On voit que la thyroide de la femme doit répondre à des besoins très variables suivant les fluctuations de son imprégnation en corps oestrogènes. L'activation de la glande correspond à des modifications morphologiques bien définies. Le révêtement des vésicules se transforme en épithélium cylindrique haut. Lorsque les besoins sont élevés, les cellules glandulaires se multiplient par mitose, la thyroide s'hyperplasie.
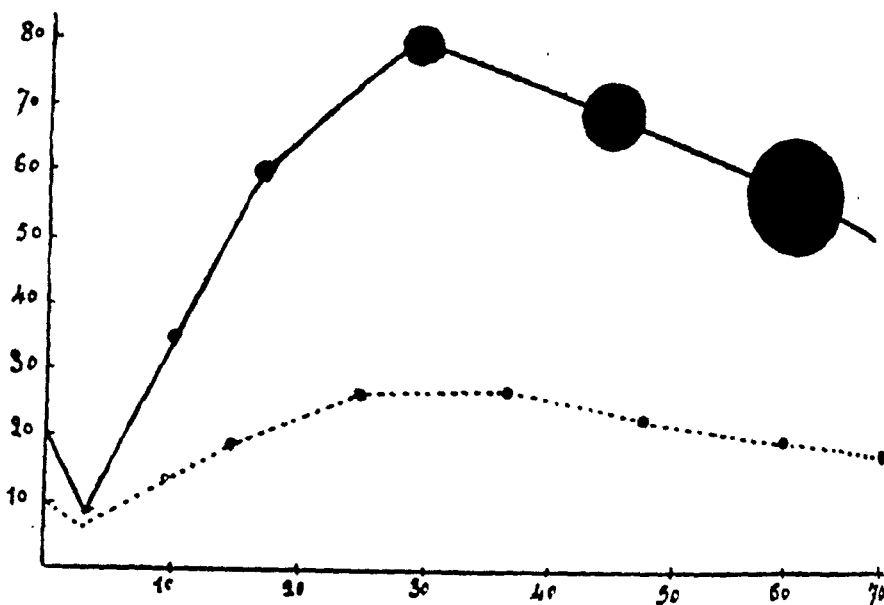
Fig. II. — Les variations de poids du corps thyroïde (en ordonnée), suivant l'âge du sujet (en abcisse), sont semblables dans les régions indemnes de goitre (courbe inférieure, en pointillés) et dans les régions goitrigènes (courbe supérieure, en trait plein). Dans ces dernières, toutefois, le poids de la glande est plus élevé, ses variations périodiques sont plus accusées et des foyers adénomateux (présentés sous forme de points) gagnent d'importance à mesure que le sujet avance en âge (d'après Aschoff).

Les graphiques statistiques d'Aschoff montrent que, tant dans les régions indemnes de goitres que dans les régions goitrigènes, la glande passe par un maximum de poids entre 25 et 35 ans, elle diminue régulièrement dans la suite. Dans les régions à endémie goitreuse, la réduction d'activité de la thyroide s'accompagne du développement de formations adénomateuses d'autant plus importantes que le sujet avance en âge (Fig. II). Ces formations constituent une modalité de mise au repos des glandes hypertrophiées.

Les régions goitrigènes réalisent certaines circonstances qui entraînent un abaissement appréciable du rendement de la thyroide. D'autres facteurs, influence familiale, carence en iode, déséquilibre minéral, avitaminoses, »kropfnoxe», etc. peuvent d'ailleurs aboutir au même résultat. L'unité de volume du parenchyme ne peut réaliser, qu'un débit sécrétoire très inférieur à la normale. La glande ne parvient à satisfaire aux besoins de l'organisme qu'en développant une hypertrophie parenchymateuse parfois considérable. Toute activation de la thyroide se traduit par l'apparition d'un goitre.

Une période de besoins élevés révolue, la thyroïde doit réduire son débit hémocrine. La mise au repos de glandes peu ou modérément hyperplasiées correspond essentiellement à des modifications microscopiques: régression de cellules glandulaires élevées et formation de vésicules colloïdes à épithélium cubique ou plat. Le stade colloïde constitue le retour à l'état »le plus voisin de la normale» que puisse atteindre une glande qui a été le siège d'une forte hyperplasie (Virchow, Marine, Bastenié). On ne doit pas perdre de vue qu'un goitre colloïde ne se développe jamais comme tel, mais succède toujours à une poussée d'hyperplasie épithéliale avec activité sécrétoire intense. La réaccumulation de colloïde avec formation de grosses vésicules est un stade secondaire. »Le goitre colloïde est un goitre parenchymateux diffus, guéri» (Wegelin).

Dans le cas des thyroïdes des régions goitrigènes, qui ont subi une hyperplasie parenchymateuse considérable, ces modifications ne sont pas toujours suffisantes. La mise au repos de la thyroïde goitreuse s'effectue souvent d'une façon peu homogène. Cette régression irrégulière est la source de la catégorie la plus importante des formations assez diverses englobées sous le terme »d'adénome thyroïdien». Il apparaît des masses noduleuses ou adénomateuses, correspondant à des zônes d'involution colloïde marquée (Fig. II). Il peut également se développer du tissu scléreux, diffus ou nodulaire. Une partie des nodules peut dégénerer en donnant lieu à des calcifications ou à des formations kystiques, parfois hémorragiques. Les formations adénomateuses sont d'autant plus importantes et durables que l'hypertrophie thyroïdienne pubertaire était plus marquée. L'apparition des nodules est de la sorte un effet indirect du facteur goitrigène (Aschoff).

On conçoit que l'étude anatomique de glandes qui ont subi successivement des hyperplasies parenchymateuses, répondant à des besoins momentanément élevés de l'organisme, et des involutions de formes diverses, montre la juxtaposition d'aspects morphologiques très variés, d'interprétation difficile,

»Adénome toxique» ou »hyperthyroidie par retard d'involution»?

L'étude de Kerley des doses d'extrait thyroidien nécessaires pour maintenir des myxoedémateuses dans un état normal fournit des renseignements précieux concernant les variations des quantités de sécrétion thyroidienne nécessaires à l'organisme féminin. Chez une de ces jeunes filles, nous voyons le besoin en thyroide passer de 15 ctg (5 ans), à 30 ctg (10 ans), (premières règles à 14 ans), 42 ctg (15 ans), 54 ctg (20 ans) et 72 ctg (25 ans). A ce moment, la malade se sensibilise assez brusquement à la thyroide, il apparait des signes d'excitation nerveuse qui font diminuer la dose à 54 ctg, puis 18 ctg, à l'âge de 27 ans. Cette dose modérée entraine encore de la tachycardie, du tremblement, de l'insomnie et un métabolisme basal élevé (+ 48 %), ce qui oblige à une nouvelle réduction de la quantité d'extrait. Cette patiente, dont l'état a nécessité l'administration journalière de 54 et 72 ctg de thyroide pendant de années, présente maintenant des signes d'hyperthyroidie nette avec une dose quatre ou cinq fois moins élevée.

On conçoit que la thyroide d'un sujet sain, placé dans les même conditions, puisse montrer une hyperplasie parenchymateus progressive (goitre de l'adolescence et de la maturité féminine puis, lors de la réduction de la demande en thyroxine, des signe d'involution globale ou circonscrite de ce parenchyme (cf. Fig. III

Une involution thyroidienne insuffisante pourra entrainer développement de signes cliniques d'hyperthyroidie résultar comme dans l'observation de Kerley, non d'une augmentation l'apport thyroxinien, mais bien de la sensibilisation acquise l'organisme. L'activité thyroidienne ne s'élève pas à un nive plus élevé que précédemment, il se produit simplement un reta à la mise au repos de la glande au moment où se réduisent les l soins du sujet.

Le syndrome »thyroide adénomateuse avec hyperthyroidie» »adénome toxique», isolé par Plummer en 1923, nous parait correspondre à une telle éventualité. On a typiquement affaire à une femme de 35 à 50 ans, qui a vu se constituer, de nombreuses années auparavant, un goitre parenchymateux, parfois volumineux, sans signe d'hyperthyroidie; parfois des nodules indurés sont apparus

dans la suite (nodules d'involution circonscrite). Progressivement, en l'absence de tout facteur causal décelable (émotion, etc) se développent des signes d'hyperimprégnation thyroidienne à l'état de pureté: tremblement fibrillaire discret, tachycardie et hypertension (parfois pris pour un trouble circulatoire primitif), amaigrissement, nervosité. Il n'est pas rare que le métabolisme basal soit notablement plus élevé (+ 35 à + 70 %) que ne le faisait présumer l'aspect clinique. L'iodémie est moins haute que dans les goitres diffus (Curtis). L'exophtalmie fait défaut.

L'énucléation des nodules est inefficace. La thyroidectomie subtotale, effectuée sans trop de retard, permet par contre une guérison parfaite, sans aucun trouble résiduel.

Le goitre est riche en iode. Sa structure ne se distingue en rien de celle d'un adénome non toxique. Il n'existe en général pas de zônes circonscrites de la thyroide dont l'hyperactivité puisse être rendue responsable d'une hyperthyroidie (Bastenié). Le nodule »adénomateux» de »l'adénome toxique» ne parait nullement une source de sécrétion »toxique», mais bien un foyer d'involution localisée à activité sécrétoire réduite, modalité de mise au repos d'une thyroide hyperplasique. Sa naissance est le résultat du bouleversement de la glande lors de régressions irrégulières (Marine). Ces constatations font dire à Dautrebande que »la cause de la transformation spontanée d'un adénome non toxique en un adénome toxique est encore très obscure». Zondek »penche vers l'opinion que, dans de nombreux cas d'adénome nodulaire, l'origine de l'hyperthyroidie est extérieure à la thyroide».

La conception que nous proposons permet de comprendre cette absence d'aspect anatomique particulier. La thyroide n'a pas donné naissance à des foyers d'hyperactivité localisée; la transformation du tableau clinique est d'origine extrathyroidienne. L'organisme a vu se réduire ses besoins en thyroxine par la sensibilisation à cette hormone qui résulte avant tout d'une diminution de son imprégnation en corps oestrogènes.

Le syndrome hyperthyroïdien de »l'adénome toxique» parait résulter d'une involution thyroidenne insuffisante lors de la dissipation d'un état de thyroxinorésistance oestrinique chronique. Il serait très désirable que cette conception puisse être vérifiée par une étude suivie du métabolisme des corps oestrogènes et de la thyroxine chez des sujets souffrant d'un »adénome toxique». Les

termes, »adénome toxique» ou »goitre basedowifié», qui ne peuvent que prèter à confusion auraient intérèt à être remplacés par des appellations plus adéquates comme »hyperthyroidie par retard d'involution thyroidienne» ou »par sensibilisation».

Il semble que ce soit la développement pris par le parenchyme thyroidien qui fasse obstacle a un ajustement rapide du débit sécrétoire de la glande et, en particulier, à une réduction importante de son activité, L'existence d'une hyperplasie parenchymateuse constitue un facteur d'irréversibilité dans les variations physiologiques de l'activité thyroidienne. Ceci nous explique la prédilection des »goitres toxiques» pour les régions goitrigènes.

La Grossesse.

L'augmentation considérable de la concentration en hormones sexuelles qui se produit au cours de la grossesse entraine une diminution marquée de l'action calorigène de la thyroxine. Bodansky et Duff (1936) remarquent que, pendant la seconde moitié de la gestation (10ème au 22ème jour), la rate tolère impunément des doses de thyroide ou de thyroxine (1 mg par jour) qui, chez les sujets normaux non gravides, entrainent une rapide perte de poids et souvent la mort. Danforth et Loumos (1936) confirment cette tolérance des rates gravides à de hautes doses d'extrait thyroidien (10 ctg pendant 16 jours). Ces animaux ne présentent qu'une augmentation minime de leur consommation d'oxygène, ils continuent à gagner du poids alors que les témoins, recevant le même apport alimentaire, voient leurs combustions s'élever considérablement et leur poids s'abaisser.

On conçoit que le maintien des combustions à la normale ou un peu au dessus de celle-ci, comme cela se produit pendant la seconde moitié de la gestation, nécessite une augmentation considérable de l'activité thyroidienne. Anselmino et Hoffmann (1931), Soule (1932) et d'autres montrent en effet que le sang de la femme enceinte contient une substance ayant les propriétés de la thyroxine, qui augmente au cours de la grossesse pour atteindre sa concentration maxima à terme. Son taux diminue rapidement après l'accouchement.

La gravidité s'accompagne régulièrement d'une augmentation de volume de la thyroide par hyperplasie parenchymateuse (Engel-

horn, Bircher, Wegelin, Schleussing et Orator, etc). L'examen histologique de la thyroïde de vache gravide montre des images d'hyperactivité évidente (Abbott). Le contenu en iode de la glande diminue (Marine — 1917).

Chez la femme, l'hyperplasie de la gestation est nette à partir du 4ème mois. La palpation de la glande révèle une augmentation de volume dans 75 % des cas selon Seitz, dans 90 % des cas selon Ruebsamen et selon Hinton. Chez 41 % des femmes cette hypertrophie est visible (Davis), ce qui témoigne d'une augmentation de volume certainement plus marquée que ne le ferait présumer l'élévation très modérée des combustions. Des données récentes, concordantes et généralement admises, notent en effet une augmentation maxima du métabolisme basal de 12 à 16 % chez la femme à terme (Plass et Yoakum — 1929, Hanna — 1938, Colvin et Bartholomew — 1939).

Il semble que la thyroïde ne soit pas toujours capable d'élever suffisamment son activité sécrétoire. Hughes (1934) constate une chute des combustions chez 77 % des femmes au 2ème, 3ème et 4ème mois de leur grossesse et chez 60 % au 5ème mois. Patterson, Hunt et Nicodemus (1937) estiment que l'hypercholestérinémie gravidique résulte d'une insuffisance thyroïdienne mise en évidence à l'occasion de l'augmentation des besoins en thyroxine de la grossesse. En l'absence de traitement, les hypothyroïdiennes reconnues voient leur état s'aggraver pendant la gestation, »les crétinoïdes, deviennent des crétines» (H. Kahr — 1939), l'évolution inverse se produit après l'accouchement. Il est bien connu que les insuffisantes thyroïdiennes traitées nécessitent une intensification de l'opothérapie thyroïdienne pour maintenir normal leur état clinique et leurs combustions pendant une grossesse (Mussey, Jennings, Davis, etc). Il faut parfois élever la dose d'extrait à 60 ctg, 1 g et plus, par jour. Dans deux cas de goitre survenu à la puberté et subissant une nouvelle poussée d'hyperplasie lors d'une première grossesse, nous avons pu administrer sans inconvénient des doses d'extrait thyroïdien de 80 ctg et de 1.20 g.

Le développement progressif de cette thyroxinorésistance relative peut entrainer l'amélioration clinique d'hyperthyroïdiennes. En effet, si un certain nombre de basedowiennes voient leur état s'aggraver pendant une grossesse (Seitz — 1913, Falls — 1929, H. Klose — 1929, Mussey et Plummer — 1931), il en est d'autres, au

contraire, chez qui on constate des améliorations remarquables (Basedow — 1840, Charcot et Dock, Kocher, Freund, Bucquet, Boisroux — 1914, M. Fabre — 1926, Hyman et Kessel — 1927, Gardiner Hill — 1929, Mussey et Plummer — 1931, Frazier et Ulrich — 1932, Kahr — 1939, Javert — 1940, etc). *Les cas graves deviennent momentanément moins sévères, les cas moyens peuvent présenter une rémission complète de leurs symptomes.* L'observation suivante est typique à ce point de vue.

Obs. — Mme S., 34 ans (1941). Pas de goitre dans la famille. Deux enfants: 11 et 16 ans. En 1939, à la suite d'un traumatisme grave, la fille ainée doit subir une néphrectomie. La mère éprouve un chagrin intense, elle passe des nuits entières sans dormir, devient très nerveuse et constate le développement rapide d'un goitre et d'une exophtalmie. Il existe de la tachycardie: 28×4, le poids tombe rapidement. Un traitement iodé n'apporte qu'une amélioration transitoire.

La patiente devient enceinte en novembre 1939. Elle souffre de vomissements abondants les 4 premiers mois, par contre, les signes d'hyperthyroïdie régressent, d'une façon remarquable. La nervosité s'atténue, la tachycardie disparait, le poids s'élève de 63 à 71 kg. Accouchement le 22 juillet 1940. Les suites de couches sont normales, toutefois la nervosité réapparait ainsi que la tachycardie. La malade perd 12 kg en un an malgré une alimentation normale. Les règles restent très espacées (6 semaines) et peu abondantes. Il existe de la diarrhée et des transpirations. M. B. + 52 %, le 26 juillet 1941, pouls à l'état de base: 28×4.

Thyroïdectomie subtotale après préparation, le 16 aout 1941 (Dr. Ectors). La malade reçoit 12 mg de thyroxine dans les 4 jours qui suivent l'intervention. Petit choc de sevrage thyroxinien le 5ème jour (t° 37.9°, pouls 26×4.) (10)

Le poids passe de 45 à 53 kg dans les 3 mois qui suivent. En janvier 1944, l'opérée pèse 55 kg. Il n'existe plus aucun signe d'hyperthyroïdie. M. B. — 1 %. On note une légère exophtalmie limitée à l'oeil gauche.

Après l'accouchement, les besoins en sécrétion thyroïdienne se réduisent considérablement. La thyroïde subit une involution colloïde pour réajuster son débit hémocrine au niveau voulu.

Exceptionnellement certains types d'hyperplasie paraissent faire obstacle à une réduction d'activité suffisante. La fin de la grossesse, ou plutôt de la lactation, est suivie du développement de signes cliniques d'hyperthyroïdie.

Obs. — Mme H., 36 ans, d'origine suisse. Pas de goitre dans la famille. Séjourne dans une région goitrigène jusqu'à l'âge de 20 ans. Ce n'est toutefois qu'à 30 ans qu'on note la présence d'un petit goitre. L'administration

d'iode, à cette époque, déclenche une poussée d'hyperthyroïdie typique, qui régresse après arrêt de la médication.

Une première grossesse, survenue en Belgique, à l'âge de 32 ans (1939), entraine une augmentation marquée du volume du goitre. L'accouchement est suivi d'un état d'hyperthyroïdie modéré, qui cède à la diodotyrosine. La patiente reste cependant très nerveuse (M. B. + 16 %).

Une seconde grossesse, en 1942, fait régresser tout signe d'excitation. La malade retrouve un équilibre nerveux et une sensation de bien être qu'elle avait perdu depuis son premier enfant. Accouchement de 2 jumelles, en octobre 1942. La mère nourrit ses enfants jusqu'en fin janvier 1943. Dans la suite, la nervosité réapparait, il se développe de la tachycardie. Le poids tombe de 65 à 59 kg. L'administration d'iode se montre nettement défavorable. M. B. + 40 %, le 21 septembre 1943. Une thyroïdectomie, en novembre 1943 (Dr Paul de Moor) permet une guérison complète.

Dans de nombreux cas, l'involution thyroïdienne rapide qui fait suite à la grossesse entraine une augmentation de volume de la thyroide, probablement par accumulation de colloide non utilisée au sein de vésicules distendues. Ce processus peut également déterminer la formation de kystes parfois volumineux.

Dans les régions à endémie goitreuse, la thyroide de la plupart des femmes montre, inscrite dans son parenchyme sous forme de nodules d'involution, les traces de poussées de grande activité correspondant à la demande sécrétoire accrue des périodes polyoestriniques et en particulier des maternités successives. Schleusing (1931), étudiant 276 thyroides féminines de plus de 50 grammes, provenant de la région de Dusseldorf, constate que les formations nodulaires se rencontrent plus souvent chez les femmes ayant eu de nombreux enfants que chez celles qui n'en ont eu qu'un seul ou n'en ont pas eu. Les thyroides multinodulaires sont d'autant plus fréquentes que le nombre de grossesses est plus élevé. Chez 34 femmes de plus de 40 ans, restées sans enfant, les nodules étaient plus fréquents chez les mariées que chez les célibataires. Six femmes ne montraient aucun nodule, il s'agissait de »virgines intactae».

Castration chirurgicale et Ménopause spontanée.

Chez l'animal, la *castration expérimentale* entraine une activation thyroidienne passagère, réaction d'alarme au traumatisme opératoire, régulièrement suivie de la mise au repos et même de l'atrophie de la glande (Engelhorn, Kolde — 1912, Andersen et Kennedy,

Bokelmann et Scheringer — 1932, Marine, Schultze — 1935, Kir_? et Loeb — 1936, etc.). Les besoins de l'organisme diminuent p_? dissipation de la thyroxinorésistance oestrinique, ce qui permet à la thyroide de réduire son débit.

Chez la femme non goitreuse, *l'ovariectomie* n'est en général suivie d'aucune manifestation clinique à rapporter à la thyroide, la glande adapte facilement son activité aux besoins réduits du sujet. Une hyperplasie goitreuse a *même pu régresser après castration chirurgicale ou radiothérapique* (Groedel — 1920). Il semble bien cependant que, dans d'autres cas, la réduction de l'activité hémocrine de la thyroide aboutisse au développement d'un goitre colloide inactif, parfois volumineux, par accumulation de sécrétion non utilisée. *L'observation suivante en constitue un exemple parmi divers autres.*

Obs. — Z. Marie, 46 ans (1944). Pas de goitre dans la famille. Pas d'enfant. Il existe une légère hypertrophie thyroidienne depuis l'âge de 35 ans; le métabolisme basal est normal. Des règles très abondantes, survenant tous les 20 jours, font pratiquer un examen gynécologique qui montre la présence d'un volumineux fibrome. Hystérectomie en mars 1942. Dans les mois qui suivent la thyroide augmente de volume, elle est le siège d'une *poussée douloureuse, »comme si c'était enflammé»,* d'une durée d'une huitaine de jours. *Le métabolisme basal reste constamment normal,* il n'existe aucun signe ni d'hyper ni d'hypothyroidie. La malade a tendance à augmenter de poids, elle présente quelques bouffées de chaleur.

Il est vraisemblable que les phénomènes douloureux passagers de cette opérée résultent d'une poussée d'inflammation aseptique au niveau d'un territoire en voie de dégénérescence (thyroidite aseptique).

La mise au repos relatif d'une thyroide hyperplasique nécessite des remaniements beaucoup plus considérables que ceux que subit une glande normale. Comme nous l'avons déjà vu, l'hyperplasie constitue un facteur d'irréversibilité qui rend malaisée une réduction à la fois importante et rapide du débit sécrétoire. Un retard d'involution lors d'une brusque sensibilisation à la thyroxine peut provoquer le développement de signes d'hyperthyroidie pure, parfois passagers, généralement sans exophtalmie. La castration chirurgicale entraine de temps en temps une réaction hyperthyroidienne de ce type (Pott — 1877, Jayle — 1897, Glaenche — 1899, L. Lévi, Bandler, Jeanneney, Dalché, Apert, Perrin et Blum,

Dreyfus, Parhon, Marañon, etc). L'observation suivante en constitue un nouvel exemple.

Obs. — T. Olga, 48 ans (1944). — Pas de goitre dans la famille. Légère hypertrophie thyroidienne depuis l'âge de 30 ans, sans modification du métabolisme basal.   Hystéro-ovariectomie pour fibrome en septembre 1941.   Peu après, la thyroide augmente notablement de volume, surtout au niveau du lobe droit.   Il survient de la nervosité, du tremblement et des battements de coeur. Le poids tombe de 72 à 44 kg. L'administration de Lugol n'apporte qu'une amélioration minime. Métabolisme basal + 45 %, en août 1942. La malade, mise au repos et traitée par des sédatifs, s'améliore très progressivement, tandis que son goitre augmente encore de volume jusqu'à atteindre la taille d'une orange. Le tremblement s'atténue, le poids remonte à 60 kg, les combustions se normalisent (M. B. + 9 %, le 16—VI—43) Il persiste toutefois une fibrillation auriculaire avec rythme ventriculaire à 20 × 4.

L'évolution de la chirurgie gynécologique vers des interventions conservant autant que possible l'activité ovarienne a rendu ces réactions hyperthyroidiennes beaucoup plus rares que jadis.

La castration radiothérapique a donné lieu à quelques observations du même genre (L. Lévi, Bandles, Jeanneney, Ujima, Novak et von Graff, etc.).

Nous avons vu, chez une femme ovariectomisée, l'interruption d'un traitement par de fortes doses d'oestrine déclencher des manifestations hyperthyroidiennes sérieuses (M. B. + 40 %), sans hypertrophie thyroidienne décelable, qui régressèrent par reprise du traitement. On sait que l'administration de corps oestrogènes est souvent favorable dans les syndromes hyperthyroidiens survenant après castration.

La *ménopause naturelle* peut s'établir selon des modalités variables. L'arrêt de l'activité ovarienne est souvent précédée d'une phase d'hypersécrétion oestrinique, période polyoestrinique, qui peut s'étendre sur des mois et même des années (B. Zondek). Béclère et Simonnet (1943) relèvent des chiffres d'oestrine élevés dans les troubles préménopausiques, tout comme dans les aménorrhées et dysménorrhées polyhormonales postpubertaires. Une telle imprégnation entraine nécessairement une augmentation des besoins en sécrétion thyroidienne. Graff et Novak constatent que la ménopause montre fréquemment l'apparition d'une hyperplasie thyroidienne surtout s'il existe un myome.

La période polyoestrinique préménopausique est suivie, brusquement ou progressivement, d'une phase oligooestrinique avec sensibilisation à la sécrétion thyroidienne, d'où réduction notable des besoins de l'organisme en cette hormone. Dans un cas de myxoedème après thyroidectomie pour Basedow, dont la guérison clinique nécessitait l'administration quotidienne de 20 à 30 ctg d'extrait thyroidien, la ménopause fut suivie de signes d'hyperthyroidie qui forcèrent à réduire la dose d'extrait à 10, puis à 6 ctg.

La mise au repos de la thyroide peut prendre des aspects divers. Généralement, il se produit de simples modifications histologiques, l'épithélium des vésicules s'aplatit, la colloide s'accumule, parfois elle donne lieu à des formations kystiques, le conjonctif interstitiel prolifère (Clerc — 1912, Noel, Goormagtich, Thomas, Florentin, Benazzi, Defitti et Nutti). Dans certains cas, le volume de la glande augmente par accumulation de colloide inutilisée. Il arrive qu'il se produise des phénomènes de dégénérescence parenchymateuse avec réaction inflammatoire et développement de tissu scléreux (von Eisesberg, Fischer). Des processus atrophiques trop marqués peuvent dépasser leur but et aboutir à une sclérose complète avec myxoedème (Gull, Curschman — 1918, Gardner, Hill et Smith — 1927, Bastenié — 1937). Une involution insuffisante, par contre, peut donner lieu à des phénomènes d'hyperthyroidie post-ménopausique, parfois passagers (Delaunay — 1899, Jouin — 1900, Pinard — 1909, Dalché — 1911, Tillman — 1919, Blamoutier — 1922, Mora et Green — 1931, Jeanneney — 1933, Tillgren et Sundgren, Marañon, etc.).

Opérations et Infections.

Il faut remarquer que certaines circonstances, indépendantes de toute variation de l'imprégnation oestrinique, peuvent réaliser une augmentation notable des besoins en thyroxine de l'organisme. Il s'agit des interventions chirurgicales et des infections. O'Keefe (1927) signale qu'il existe cinq périodes de l'existence de la femme où se manifestent avec prédilection des signes cliniques et métaboliques d'hypothyroidie qui rendent une opothérapie thyroidienne nécessaire. Ce sont la puberté, la grossesse, la ménopause, les opérations et les infections.

Toute intervention chirurgicale est suivie d'une augmentation immédiate de l'excrétion de produits iodés (Curtis), ce qui correspond vraisemblablement à la dégradation d'une quantité élevée de sécrétion thyroidienne lors de la maladie opératoire. La thyroide répond à ces besoins accrus par une activation de son parenchyme, Selye note une hyperplasie thyroidienne parmi les modifications organiques qui font suite aux traumatismes («réaction d'alarme»). Une de nos patientes, porteuse d'un goitre colloide et d'un carcinome mammaire, vit son goitre disparaitre à peu près complètement dans les jours qui suivirent l'amputation large du sein, probablement par résorption et utilisation des masses colloides vésiculaires.

On conçoit que l'hyperthyroidien grave, qui affronte la maladie opératoire avec une thyroide dont la réserve colloide est pauvre, ne parvienne pas toujours à faire face à ce brusque excès de consommation et développe parfois des accidents hypothyroxémiques aigus (8, 10). La gravité des crises hypothyroxémiques qui font suite à certaines thyroidectomies pour Basedow parait résulter de ce que la suppression de l'apport thyroxinien dû à la résection survient au moment précis où le traumatisme opératoire entraine un accroissement de la demande en thyroxine. Nous avons montré ailleurs que ces accidents redoutables peuvent être prévenus par administration systématique de cette hormone (9, 10). [1]

Les affections fébriles entrainent également une augmentation de l'excrétion iodée (von Fellenberg — 1923), probablement par

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[1] Les crises aigues, qu'elles soient post-opératoires ou spontanées, peuvent s'accompagner de modifications électrocardiographiques caractéristiques de la carence thyroidienne: inversion transitoire de l'onde T (Hamburger —1917, Krumbhaar —1918, Hamburger, Lev, Priest et Howard —1931, Parade et Haas —1931, Kammerer et Obermaier —1932, etc), ralentissement momentané de la conduction auriculo-ventriculaire (Post-thyroidectomie: Lewis —1913, E. Simon —1927, Davis et Smith —1933, Meyer et Stahl —1934, Parade · 1937, Crises spontanées: Merklen —1881, De Vries Relling —1915, Kessel et Hyman —1925, Davis et Smith —1933, etc). Le traitement thyroxinien post-thyroidectomie prévient ces manifestations hypothyroxémiques. Dans des cas de thyroidectomies très larges, nous avons pu cependant constater une inversion passagère de l'onde T, non après l'opération, mais dans les quelques jours qui suivent un sevrage thyroxinien brusque.

A noter que la prévention ou le traitement des crises aigues post-thyroidectomie par l'extrait thyroidien et la thyroxine ont déjà été préconisés par G. W. Crile (1922), Kessel et Hyman (1925), John Rogers (1926), Santee (1927), Dinsmore (1937), Raoul Berger (1939). J. Rogers (1937) remarque que, dans cette condition très particulière, l'extrait thyroidien manifeste une action sedative «plus efficace que celle de la morphine», ce que nous avons pu confirmer à diverses reprises (8).
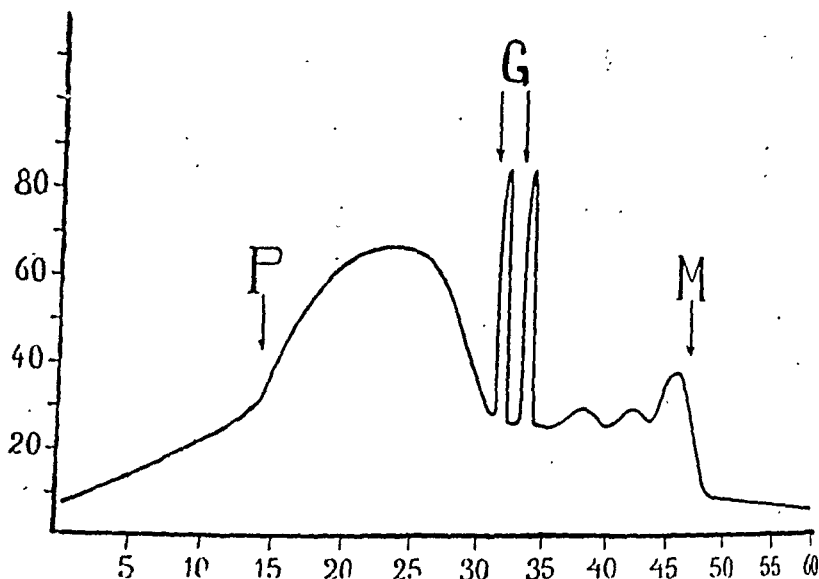
Fig. III. — *Représentation schématique des besoins en sécrétion thyroïdienne d'une femme ayant présenté deux grossesses.*

En abscisse, le temps.   En ordonnée, la quantité de sécrétion thyroïdienne exprimée en extrait sec.

La puberté, à 14 ans (P), détermine une augmentation considérable des besoins de l'organisme, qui passent par un maximum entre 20 et 25 ans. Deux grossesses, à 31 et 33 ans (G), amènent une élévation marquée de la quantité de sécrétion thyroïdienne utilisée, qui cesse brusquement à la disparition de l'état gravide.   La ménopause (M) entraîne une augmentation momentanée des besoins, suivie d'une dépression profonde.   La disparition de l'imprégnation oestrinique réduit à un niveau minimum les besoins en sécrétion thyroïdienne.

utilisation d'une quantité élevée de sécrétion thyroïdienne. Les modifications de la thyroïde ont été étudiées par de nombreux auteurs (Roger et Garnier — 1898, Toni — 1900, Kashiwamura — 1901, de Quervain — 1906, Sarbaud — 1906, Farrant — 1914, Mc Carrison — 1917, Simmonds — 1917, Cole et Womack — 1928, Leffmann — 1932, Thomas — 1934, Selzer — 1935).   On note une hyperhémie. L'épithélium prend un aspect actif, il prolifère et se ramifie dans les vésicules. La colloïde subit une fonte rapide et tend à disparaître.   Le contenu en iode de la glande diminue fortement (Aschenbacher — 1906).   On comprend que toute infection survenant chez un hyperthyroïdien sérieux, à réserve colloïde réduite, puisse déclencher un état de crise hypothyroxémique.

La scarlatine, le rhumatisme articulaire aigu, la fièvre typhoïde, la tuberculose pulmonaire dans ses formes aigues, entraînent une résorption particulièrement active de la colloïde thyroïdienne.

L'infection guérie, la glande réaccumule de la colloïde, ce qui aboutit parfois au développement d'un goitre peu actif. Il n'est pas exceptionnel de voir une pyrexie prolongée être suivie d'une augmentation de volume de la thyroïde. Une involution insuffisante parait pouvoir réaliser un syndrome clinique d'hyperthyroïdie. Nous avons eu l'occasion de traiter une hyperthyroïdie grave qui avait fait suite à une atteinte de rhumatisme articulaire aigu. La thyroidectomie permit d'obtenir une guérison parfaite.

L'activation thyroïdienne des affections fébriles semble répondre essentiellement à la consommation d'une quantité élevée de thyroxine par les mécanismes thermorégulateurs à activité modifiée par la fièvre. Elle fait défaut chez les poikilothermes (reptiles), même lorsqu'ils présentent des septicémies graves (J. A. Murray — 1918).

On voit que, si l'on excepte les états pathologiques, généralement passagers, que peuvent créer des traumatismes ou des infections, les besoins en sécrétion thyroïdienne de l'organisme féminin varient dans le même sens que son imprégnation en corps oestrogènes (Fig. III). La puberté, la maturité féminine, les grossesses, parfois la préménopause, exigent une augmentation souvent considérable de l'activité thyroïdienne pour compenser la diminution d'action calorigène de la thyroxine due à l'élévation du taux des oestrogènes (thyroxinorésistance oestrinique). Il se développe fréquemment une hyperplasie thyroïdienne parenchymateuse sans signe clinique d'hyperthyroïdie. Lorsque cet effort sécrétoire reste inférieur aux besoins accrus de l'organisme, il peut apparaitre un syndrome clinique d'hypothyroïdie quoique l'activité thyroïdienne soit plutôt en voie d'accroissement (hypothyroïdie de la puberté et de la grossesse).

La période polyoestrinique physiologique révolue, la sécrétion thyroïdienne récupère une action calorigène élevée. La thyroïde doit diminuer son activité sécrétoire. Les glandes hyperplasiées montrent des phénomènes d'involution parenchymateuse. Un manque de freinage de la sécrétion, une involution trop lente, peut entrainer le développement de signes cliniques d'hyperthyroïdie quoique l'activité thyroïdienne soit plutôt en voie de réduction (»hyperthyroïdie par sensibilisation», »adénome toxique» ou »goitre basedowifié»).

Le maintien des combustions et de l'excitabilité nerveuse à la normale exige un parallèlisme relatif de débit thyroïdien et de l'activité ovarienne. Nous retrouvons ici la »sympathie thyro-ovarienne» des anciens auteurs.

Remarquons à ce propos qu'une définition statique d'une activité thyroidienne normale ne se conçoit pas. La thyroïde normale est celle qui s'adapte rapidement et sans défaillance aux besoins variables de l'organisme, qui augmente son débit dans la mesure voulue lorsque la demande est élevée et le réduit lorsqu'elle est moindre. L'activité thyroidienne n'est normale qu'en fonction d'un équilibre polyhormonal, où les corps oestrogènes paraissent jouer le rôle primordial [1].

Les Mécanismes thyreorégulateurs.

Il nous reste à examiner par quel mécanisme une élévation de ces corps oestrogènes détermine une thyroxinorésistance relative et quel est l'appareil régulateur qui déclenche et controle l'activité compensatrice de la glande thyroide. L'étude de ces questions constitue la partie la plus délicate de notre exposé, car elle nous entrainera nécessairement a réenvisager le mécanisme de l'action de la thyroxine sur les combustions et à formuler de nouvelles hypothèses [2].

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[1] Il est généralement impossible à l'histologiste de faire un diagnostic d'hyper ou d'hypothyroidie d'après l'aspect actif ou non des vésicules thyroidiennes. L'évaluation d'une fonction nécessite la connaissance d'une norme dont elle s'écarte. La thyroide doit normalement faire face à des besoins physiologiques très variés qui la font passer successivement par des périodes d'activité marquée et de repos. L'anatomiste ne peut que se borner à décrire les aspects observés sans pouvoir émettre de diagnostic clinique. Des vésicules à épithélium haut, ramifié, très actif peuvent tout aussi bien se rencontrer dans un goitre juvénile, une hyperplasie de grossesse une maladie d'Addison ou une pyrexie, que dans un Basedow. Des éléments thyroidiens peu actifs peuvent appartenir à un goitre nettement »toxique» ou à un Basedow dont l'iode a fait involuer la structure thyroidienne tout en laissant subsister un tableau clinique d'hyperthyroidie imparfaitement amélioré.

[2] Divers auteurs paraissent considérer comme acquis que la sécrétion thyroidienne va baigner toutes les cellules de l'organisme et y intervient directement pour activer les combustions. Cette conception est peu acceptable. Le temps de latence nécessaire pour que l'action hypermétabolique se manifeste indique certainement un mode d'action plus complexe. Harrington estime que »l'hormone thyroidienne agit probablement plutôt en mettant en marche un mécanisme compliqué qu'en influençant elle même, par voie directe, les divers processus de l'organisme.»

Il semble bien, d'autre part, que le produit de sécrétion de la thyroide soit

L'inaction, parfois complète, de la thyroxine, dans l'insuffisance hypophysaire grave, chronique, nous a amené à la notion que cette hormone doit être fixée par un substrat hypophysaire pour pouvoir exercer son action sur les centres thermogénétiques du diencéphale (11). Nous avons montré ailleurs que cette théorie, qui rend compte de l'existence de certains états de thyroxinorésistance, permet également de donner une interprétation logique, parfaitement cohérente, de nos connaissances de la cytologie et de la physiologie de l'hypophyse dans les troubles thyroïdiens (12).

L'hypophyse paraît contenir, au sein d'éléments chromophobes, une substance »thyroxinaffine», très voisine de la thyréostimuline, fixant électivement la sécrétion thyroïdienne sanguine. Le complexe pituito-thyroxinien obtenu, qui s'identifie probablement aux granulations éosinophiles, migre vers les centres diencéphaliques dont il règle le tonus fonctionnel.

Une carence en sécrétion thyroïdienne entraine une réduction des éosinophiles; la substance »thyroxinaffine» (thyréostimuline) inutilisée s'accumule au niveau d'éléments chromophobes caractéristiques (cellules de thyroïdectomie), elle passe ensuite dans la circulation générale et peut même être décelée dans les urines. Cette libération de thyréostimuline excite le système de commande de la thyroïde et tend à rétablir une activité thyroïdienne plus élevée.

Un excès de sécrétion thyroïdienne sature la totalité de la substance »thyroxinaffine» (thyréostimuline) en donnant un complexe où la fonction excitothyroïdienne de la thyréostimuline est bloquée par la thyroxine. L'hypophyse, riche en éosinophiles, perd tout pouvoir excito-thyroïdien. En l'absence d'autre mécanisme d'excitation, la thyroïde du sujet est mise au repos, ce qui

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une globuline iodée, substance particulièrement peu capable de diffuser dans les tissus.

Nous pensons que la sécrétion thyroïdienne se fixe au niveau d'organes très vascularisés, pourvus d'une affinité élective à son égard, qui lui est conférée par un »substrat thyroxinaffine» particulier. Le tissu hypophysaire paraît procéder de la sorte à l'extraction de la sécrétion thyroïdienne du courant sanguin. Il est possible que d'autres organes, comme les ovaires, par exemple, dont on connaît la richesse en iode, soient doués de la même propriété. Remarquons que l'utilisation d'une certaine quantité de thyroxine par des ovaires actifs ne peut qu'accroître les besoins en sécrétion thyroïdienne de l'organisme féminin.

tend à rétablir une imprégnation thyroïdienne moins élevée. Cette neutralisation physiologique de la thyreostimuline par la thyroxine constitue le chaînon hypophysaire de la régulation thyroïdienne; elle tend à maintenir l'activité thyroïdienne à un niveau constant en rapport avec la richesse de l'hypophyse en substance »thyroxin-affine» (thyreostimuline).

La chute rapide des combustions et la diminution de l'action calorigène de la thyroxine qui s'observe chez les sujets soumis à une imprégnation oestrinique élevée semble résulter d'un blocage partiel du système hypophyse-diencéphale par action directe de l'hormone sexuelle à son niveau. Cette fixation de corps oestrogènes parait entraîner une diminution du pouvoir de fixer et d'utiliser la thyroxine au niveau du complexe pituito-diencéphalique (thyro-xinorésistance oestrinique), vraisemblablement par concurrence hormonale en présence d'une quantité limitée de substrat hypo-. physaire. Cette interprétation s'accorde avec les conclusions des travaux expérimentaux de Sherwood, de Gessler et de Danforth, Greene et Ivy, qui attribuent à un effet hypophysaire la diminution de l'action calorigène de la thyroxine des animaux injectés d'oestrine, ce qui implique nécessairement que l'action de la thyroxine sur les combustions soit susceptible d'être modifiée, comme nous le soutenons, par altération du fonctionnement hypophysaire.

Quel est, dans ces conditions, le mécanisme qui assure l'augmentation de l'apport en thyroxine nécessaire au maintien des combustions et de l'excitabilité nerveuse à leur valeur normale. Le blocage de la glande pituitaire par l'oestrine parait exclure une excitation d'origine hypophysaire. L'hypothèse, émise par Anselmino (1934) et par Pratt (1936), d'une hormone ovarienne ayant là propriété d'exciter là thyroïde semble peu vraisemblable.

Au cours de plusieurs centaines de mesures de métabolisme basal chez des femmes présentant une hypertrophie thyroïdienne sans signe clinique ni d'hyper ni d'hypothyroïdie, nous avons été frappés de la valeur presque constamment normale des résultats obtenus. Loin d'apporter une perturbation aux combustions, le développement du goitre parait, au contraire, leur permettre de garder une valeur idéale.

Il semble qu'un mécanisme régulateur central, agissant vraisemblablement par voie nerveuse, règle à chaque instant l'activité

thyroïdienne à la valeur précise qui maintient le métabolisme à son taux standard. La normalisation, presque constante, des combustions de sujets ayant subi des résections thyroïdiennes d'importance très variable conduit à des conclusions identiques.

Tout se passe comme si l'organisme des homéothermes disposait d'un appareil sensible inconscient, automatique, lui permettant d'apprécier la valeur de ses combustions et, en particulier de son métabolisme basal, et de la comparer à une courbe étalon, remarquablement fixe, caractéristique de la race et du sexe, inscrite dans ses centres nerveux, indiquant les modifications régulières des combustions au cours de l'existence.

Une chute du métabolisme en dessous de la normale entraîne rapidement un réflexe d'activation thyroïdienne. Une élévation des combustions suscite au contraire une réduction de l'activité sécrétoire. Ces réactions ne sont probablement que des cas particuliers parmi l'ensemble des réflexes neurohumoraux qui assurent la constance thermique [1], elles constituent le chainon nerveux de la régulation thyroïdienne.

Insistons sur le fait qu'une déviation du métabolisme basal, dans un sens ou dans l'autre, ne constitue nullement une «mesure» de l'activité thyroïdienne, mais, en l'absence de troubles extra thyroïdiens, indique simplement que l'activité de cette glande n'est pas adaptée aux besoins momentanés du sujet. Malgré ces réserves et la complexité des facteurs qui contribuent à déterminer la valeur des combustions, l'estimation du métabolisme basal reste cependant le meilleur critère d'appréciation, non de la valeur absolue de

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[1] On ne doit pas perdre de vue, en étudiant les réactions thyroïdiennes, que cette glande, qui constitue un des organes essentiels de la régulation thermique, est soumise au controle des centres thermorégulateurs. Une augmentation de la déperdition thermique, par exposition au froid, entraine une hypothermie à laquelle le sujet réagit par l'élévation de sa thermogénèse et par une stimulation plus ou moins précoce de sa thyroïde. La glande montre un aspect hyperactif avec chute de son contenu en iode. La chaleur détermine des modifications inverses (Mills — 1918, Ludford et W. Cramer — 1928, Dietrich et Schwiegk — 1932, Kenyon — 1933, Kuschinsky — 1935, Woltkewitch — 1936, etc.).

Nous avons vu que la fièvre, état d'homéothermie nouveau fixé à un niveau plus élevé, entraîne des besoins accrus en sécrétion thyroïdienne et une activation de la glande.

La poussée de prolifération thyroïdienne, qui fait suite à la naissance et aboutit, dans les régions à goitre endémique, à la constitution du goitre du noüveau né (cf. Fig. II.), répond probablement à la brusque élévation des besoins en thyroxine due à la mise en activité des fonctions végétatives thermorégulatrices et autres.

l'activité thyroïdienne, mais de sa »normalité» par rapport à la demande de l'organisme.

Des combustions standard paraissent pouvoir correspondre à des débits thyroïdiens très variés. Même si une méthode nouvelle, tirée par exemple de l'étude des bilans d'iode, nous permettait de connaître avec précision le quantité de thyroxine secrétée par 24 heures, il nous serait difficile, de juger si la valeur obtenue correspond ou non aux besoins du sujet.

Quoique cette question ait été l'objet de nombreuses controverses, il paraît vraisemblable que la transmission des influx centraux à la thyroïde se fait par la voie du sympathique cervical. On sait que l'excitation de cette voie nerveuse détermine l'apparition d'un courant d'action au niveau de la glande (électrothyréogramme) avec diminution de son contenu en iode et élévation de l'iodémie (Helin et Ziliacus — 1941).

Résumé et Conclusions.

L'action de la sécrétion thyroïdienne sur les centres neurovégétatifs et métaboliques paraît nécessiter la présence d'un substrat hypophysaire »thyroxinaffine», très voisin de la thyréostimuline.

L'établissement d'une imprégnation oestrogène élevée entraine une diminution marquée de l'action calorigène de la thyroxine, probablement par blocage oestrinique du complexe pituito-diencéphalique.

Cette thyroxinorésistance polyestrinique se manifeste dans toutes les circonstances où le taux des oestrogènes prend une valeur élevée (puberté, maturité féminine, grossesses, fibromatose utérine, préménopause). Elle entrainerait une dépression de l'excitabilité nerveuse et une chute des combustions si elle n'était régulièrement compensée par une augmentation physiologique de l'activité thyroïdienne. La thyroïde montre des signes histologiques d'activation, souvent elle s'hyperplasie pour augmenter son débit.

La période de thyroxinorésistance révolue, la glande se met au repos. La colloïde se réaccumule au sein de vésicules peu actives, parfois il se produit des phénomènes de sclérose localisée.

Une activation thyroïdienne insuffisante peut entrainer l'apparition de signes cliniques d'insuffisance thyroïdienne. Un retard

d'involution peut, au contraire, donner naissance à des signes d'hyperthyroidie.

Il semble que l'activité thyroidienne soit essentiellement controlée par le jeu de centres régulateurs du métabolisme, agissant par voie nerveuse, qui tendent à maintenir constamment les combustions basales à leur valeur normale.

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Calory-Supply and Basal Metabolism.

By

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It is evident that the calory-supply greatly influences the combustion which occurs in the living organism; yet, in general, too little attention is paid to it.

In 1900 Svenson (1) and Magnus Levy (2) already pointed out the fall of the basal metabolism which accompanies chronic undernutrition, as resulting of wasting infectious diseases.

In 1907 Benedict (3) amply discussed the influence produced by fasting on the various physiological processes in the professional faster Levanzin. He stated that fasting caused a slight increase in basal metabolism at the outset and then a sharp fall, both of basal metabolism and pulse rate. This fall reached its lowest value after three weeks and was then 30 per cent. below the initial value. In the fourth week however the metabolism gradually increased, resulting from the stores in the body being consumed then and the protein reserves touched.

Allen and Du Bois (4) and Joslin (5) too, stated falls in the metabolism of as much as 20 per cent. caused by fasting.

The point is now whether the findings obtained in cases of fasting can be compared with those connected with under-nutrition. Formerly it was thought that there was an essential difference between them. It was assumed that owing to the oxidation of the fat-stores an acidosis appeared, which was never brought about by starvation. It was believed that this acidosis had a stimulating effect on the metabolism and partly counterbalanced the fall

caused by fasting. It has been proved, however, that this acidosis has hardly any influence on metabolism and moreover, that starvation, too, is accompanied by a slight acidosis; in the latter case the fat-stores are indeed touched as well, so that there is only a difference in degree between fasting and starvation and the effects of fasting may therefore certainly be compared with those of starvation. There are also investigations where the connection between starvation and basal metabolism manifests itself directly.

Zuntz (6) and Loewy (6 and 7) compared their own metabolisms before the Great War with those in 1916, so in the middle of the war, when there was a manifest starvation. Zuntz found his own basal metabolism decreased by 7.5 per cent. and Loewy by 12.2 per cent. per square metre body surface.

In connection with the food-reduction problem in Europe in the Great World War, Benedict, Miles, Roth and Smith (8) investigated its influence in two groups of American students. Squad A. got a normal diet of 3200 to 3600 Calories a day and was then put on a diet of 1950 Calories with the exception of Sundays, which slightly impairs the importance of the results. In the course of the investigations, which were carried out very minutely, it was distinctly found that in consequence of a comparatively slight starvation the metabolism fell both per kilo. body weight and per square metre body surface. In Squad A. an average fall of metabolism of 7.3 per cent. was found after no more than ten days and finally even a fall of 23 per cent. per square metre body surface.

In Squad B., which was put on a diet of 1375 Calories per day, a fall of 24.7 per cent. was found after a few weeks. Starvation however not only causes a fall of metabolism, but also of the systolic and diastolic pressure of the blood, of the pulse rate and the respiration rate.

Master, Jaffe and Dack (9) found in heart-patients on a diet of 800 Calories a reduction of the basal metabolism of 15 to 35 per cent. after two or three weeks.

From all this it appears that starvation can highly influence the basal metabolism and that after ten to fifteen days a marked reduction can manifest itself.

Benedict found an average fall of 7 per cent. in the metabolism on a diet of 1950 Calories after ten days and Master c.s. on a diet of 800 Calories a fall of 15 to 35 per cent. after a fortnight.

For the clinic it is important to investigate how soon a rather drastic restriction of Calories can make its influence on metabolism felt, since in the clinic short-continued restrictions of the calory-supply are regularly met with as e.g. in patients with gastric ulcers, in patients vomiting for some days, in patients who due to illness take hardly any food, in patients who have been put on a test diet for diabetics, etc.

In all these patients metabolism will be reduced and it is important to take this into account in the experiments. About the influence of starvation on the metabolism little information is available.

Grafe (10) describes three patients whose metabolism is said to have been raised by over-nutrition, but in general we may say that excessive feeding is rare, and its influence on metabolism not so marked as that of starvation.

To investigate the influence which a short-continued but rather marked starvation has on metabolism we have investigated the course of the metabolism in six patients who on account of a duodenal or ventricular ulcer had been put on a special Sippy-diet.

The investigations were carried out in Noyons' respiration chamber (11) in combination with Haldane's apparatus for gas-analysis. The glass respiration-chamber has a capacity of 600 litres and the patient is lying in it quietly on a bed. The air in the chamber is constantly ventilated by the supply of fresh air. The temperature is kept constant at exactly 20° Centigrade by means of warm and cold water heating. This has the great advantage that the patients lie in a quiet, soundless room and are not hindered by mouthpieces, valves and such like which cause a troubled and non-physiological respiration and practically always give rise to important errors during the experiment. The gases in the outgoing air are analysed in the Haldane's apparatus. The results obtained by means of this apparatus are very accurate and, as we have frequently found, more satisfactory than those obtained by means of volume-recording metabolic apparatus.

In the first week of their diet-cure, when the most appreciable and most important changes are found, the patients were examined mostly three times; the rest of the time they were examined once a week. The investigation was always carried out twelve to
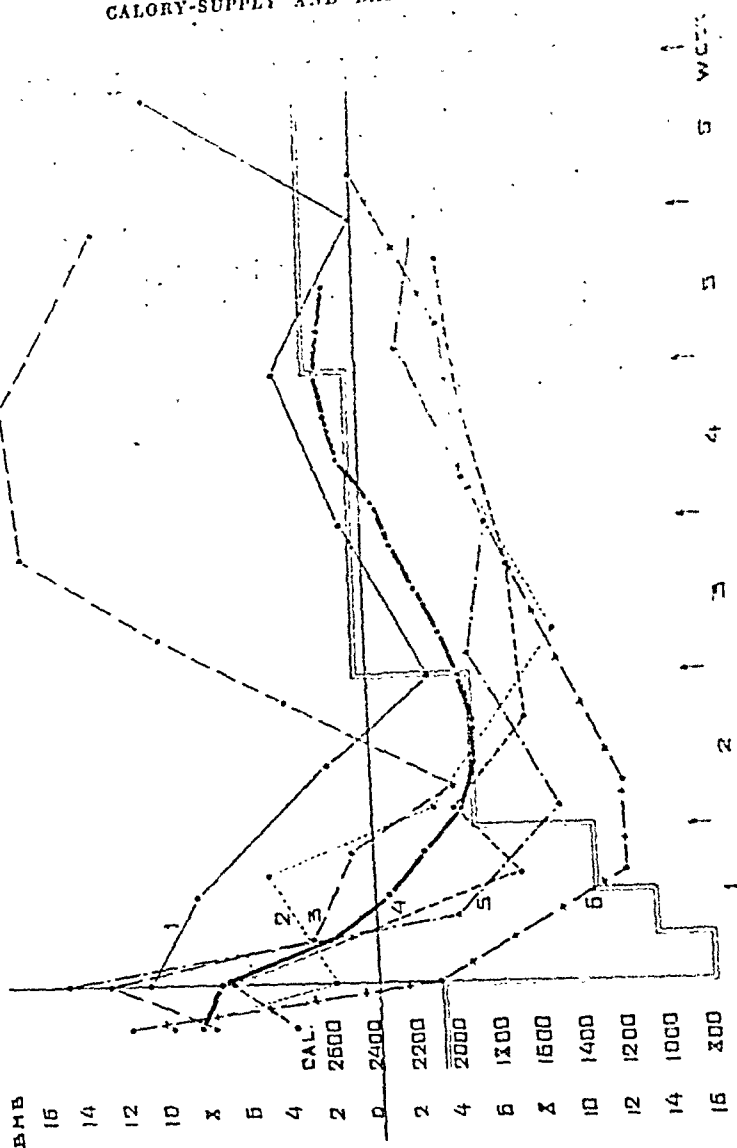
Fig. 1.

fourteen hours after the last meal. The diet, which was identical
for all patients and adapted to war-circumstances, contained 820
Calories during the first and second days, 1080 Calories during
the third and fourth days, 1360 Calories during the fifth, sixth
and seventh days; in the second week it contained 1930 Calories,
in the third and fourth weeks about 2460 Calories and in the fifth
and sixth weeks about 2670 Calories per day.

In figure I the metabolic rates of the six patients have been

registered. The bold dot and dash line gives the arithmetical
average of the six curves.

The first thing one sees here is that the metabolism, even before
the diet-curve was begun, shows a slight tendency to fall. This
can be accounted for by the fact that even under the most favour-
able technical circumstances the second registration of the basal
metabolism is lower than the first since the patients are quieter.
During the first week of the cure an appreciable reduction of
about 11 per cent. in the metabolism occurs, which is evidently
connected with the great restriction of calory-supply in that week.
In the middle of the second week the fall in the metabolism reaches
its lowest value of 13 per cent. below normal.

With a supply of about 1900 Calories in the second week the
metabolism is more or less constant. This indicates that for resting
individuals a caloric value of about 1900 is the limit of the calory-
requirement. Loewy came to the conclusion that this limit is about
2000 Calories.

After the second week the basal metabolism can be seen to
rise regularly in proportion to the increased calory-supply. This rise,
however, takes more time than the fall. This is presumably caused
by the fact that the decrease of the calory-supply occurs more
abruptly than the increase afterwards and that consequently a
more gradual adaptation of the organism is possible.

We have, besides, registered the basal metabolism in a large
group of patients at the beginning of the Sippy-cure and invariably
found remarkably low values during the first fortnight of the cure.
In only one patient no fall in the metabolism during the Sippy-
cure was found. This patient was a small, thin woman whose nor-
mal metabolism was already low and who took no more than 1200
Calories per day. In this patient we found, before the cure, —5.5
per cent.; 4th day 1st week —3 per cent.; 1st day 2nd week —3
per cent.; 4th day 2nd week —2 per cent.; 4 th day 3rd week —5.5
per cent.; 4th day 5th week —5.5 per cent. Probably her metabo-
lism did not show a distinct fall since for her a diet containing 800
to 1100 Calories did not imply an appreciable under-nutrition.

After vomiting, too, when a drastic restriction of food sets in,
metabolism is greatly reduced. So e.g. in a woman-patient aged 24,
we found on March 28, 1942 a metabolism of —1 per cent., March
30 one of + 2 per cent. In the following days the patient was un-

well and vomited all food for a few days in succession. April 8 we found, as a result, a metabolism of —15 per cent. and April 9 one of —17 per cent. In another patient, too with an atrophic arthritis, we saw metabolic rates of +21 per cent. and +19 per cent. before the experiment; after that we put him on a diet of about 700 Calories and next on May 1st 1942 we found a metabolism of +14 per cent.; May 2 one of +6 per cent. and May 4 one of +10 per cent. This proves that short-continued rather serious starvation can already lower the metabolism in a single day.

In the course of the present war the influence of long-continued slight under-nutrition on the basal metabolism has been quite perceptible in the metabolic results which we calculated from experiments on our patients, 80 per cent. of whom are clinical and 20 per cent. policlinical patients. For that purpose we have compared the metabolic results obtained in the clinic in 1939, that is before the present war, with those of 1942 and 1943, both on 900 patients.

The technique was the same all through those years and the work was done by the same analyst. The results were registered by means of Noyons' respiration chamber in combination with Haldane's gas-analysing apparatus. The patients were classified in groups with a gradual rise of 5 per cent., according to the level of their metabolism.

First came a group with a metabolism between —40 per cent. and —35 per cent. and at last a group with one between +95 and +100 per cent., and it was ascertained how many per cent. of the number of patients examined during the years 1939, 1942 and 1943 belonged to the different metabolic groups.

Figure II schematically indicates the spread of the metabolic results for the different groups in the different years. From this it appears that before the present war the average normal metabolism was about +8.5 per cent. This is in accordance with the well-known fact that in the technique applied by us in Holland, the zero of metabolism is 7 or 8 per cent. higher than the Harris-Benedict values.

Naturally the calory-supply of the food varied greatly, but we may safely estimate it to 2500 to 3000 calories per day. The average calory-supply for the English middle classes was computed to about 3070 calories per day.

In 1941 the caloric value of the food in consequence of rationing
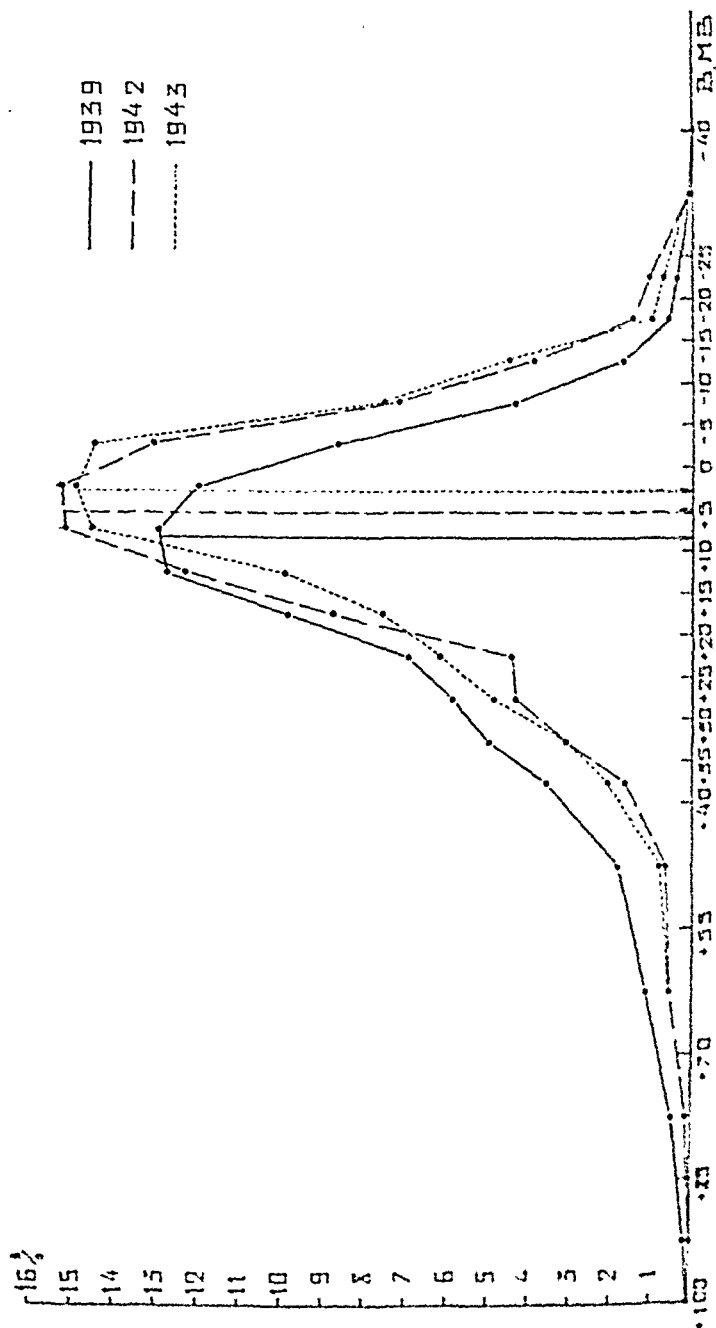
Fig. II.

regulations fell to about 1800 and in 1942 to 1610 calories per day. The average metabolism in 1942 showed, naturally, a distinct reduction of about 3 per cent. and reached the level of +5.5 per cent. In 1943 the calory-supply was not reduced any further and even increased to 1650 calories per day but in spite of this we found a further reduction of the average metabolism to +3 per cent. That in 1943 the metabolism was still more reduced though the calory-supply was not lower than in 1942 is, in our opinion, due to the longer period of under-nutrition to which the organism has gradually been adapted. The consumption of the different reserves may have contributed to it as well.

Thus figure II clearly shows a total shift of the metabolism to a lower level. Moreover it can be noticed that the number of metabolic values near the normal level has grown considerably; formerly this number of values amounted to 13 per cent.; in the course of the present war it has increased to 15 per cent. The most striking feature is perhaps the great reduction of the number of high metabolic values whereas the number of low metabolic values has not increased proportionally. That the number of high metabolic values has declined is also demonstrated in the clinic where the number of patients with hyperthyroidism and Basedow disease in the course of the war has considerably been reduced.

In 1938 the number of hyperthyroidism-patients amounted to 33.2 per thousand hospital-patients. In 1939 the number was 33.7 per thousand, in 1942 a sharp fall set in to 15.5 per thousand and in 1943 the number even dropped to 8.8 per thousand, so to about one fourth of the number of patients before the war. This shows that a reduced calory-supply can counteract the manifestation of hyperthyroidism.

The question is now how the fall in the metabolism as a result of short-continued drastic and the long-continued slight under-nutrition is brought about.

Former investigators looked for an explanation of the fall in the metabolism in the loss of nitrogenous elements by the body, which loss decreased the quantity of stimulating substances in the tissue fluids. This theory, however, though it looked very attractive, could not maintain itself, for already Benedict (8) was able to demonstrate that there was no strict parallelism between the loss of nitrogenous substances by the body and the fall of metabolism.

Personally we have been able to state that a patient who, on starvation, had lost 36 grammes of nitrogen in 12 days, showed a fall of 8 per cent. in his metabolism, while in another patient who lost 34 grammes of nitrogen, the metabolism showed a fall of 14.5 per cent. in the same period. A third patient lost 18 grammes of nitrogen in 12 days and showed a reduction of 8 per cent. So here no parallelism either.

Thannhauser (13), Lusk (14), Plummer and Vogt (15) and Mc. Carrison (16) point out that in consequence of a reduced food supply the endocrine organs atrophy and become deficient and that thus a reduction in the metabolism is brought about. In the first place the connection between starvation and the activity of the thyroid gland will probably have to be made clear. In his experiments on under-nutrition Mc. Carrison (16) found a distinct atrophy of the thyroid gland. Vogt (15) on starvation it rats found an atrophy of the cells lining the thyroid vesicles and a flattening of the nuclei, together with an accumulation of colloid in the vesicles. The metabolism is one of the principal manifestations of the activity of the thyoid and it is therefore likely — also in view of the experiments quoted — that starvation impairs the activity of the thyroid gland and of the metabolism.

It will, presumably, be possible to get an idea of the thyroid function from the eagerness with which radio active iodine injected into the body is absorbed by the thyroid, so from the iodine metabolism.

We have tried to find out whether in symptoms of deficiency of other endocrine organs manifest themselves on starvation. In the first place we drew our attention on the suprarenal gland. It is known that this gland, and especially the medulla, has together with the central nervous system and the spinal cord, an important influence on the blood pressure. The function of the suprarenal cortex is closely connected with the sodium content of the serum. It did already strike Benedict that in students put on a restricted diet a fall in the systolic and diastolic blood pressure becomes manifest.

We have also tried to find out whether the short-continued starvation in the Sippy-patients occasioned any fall of the blood pressure. To this purpose we determined the pressure a few times in the morning directly after the determination of the metabolism and took the average.
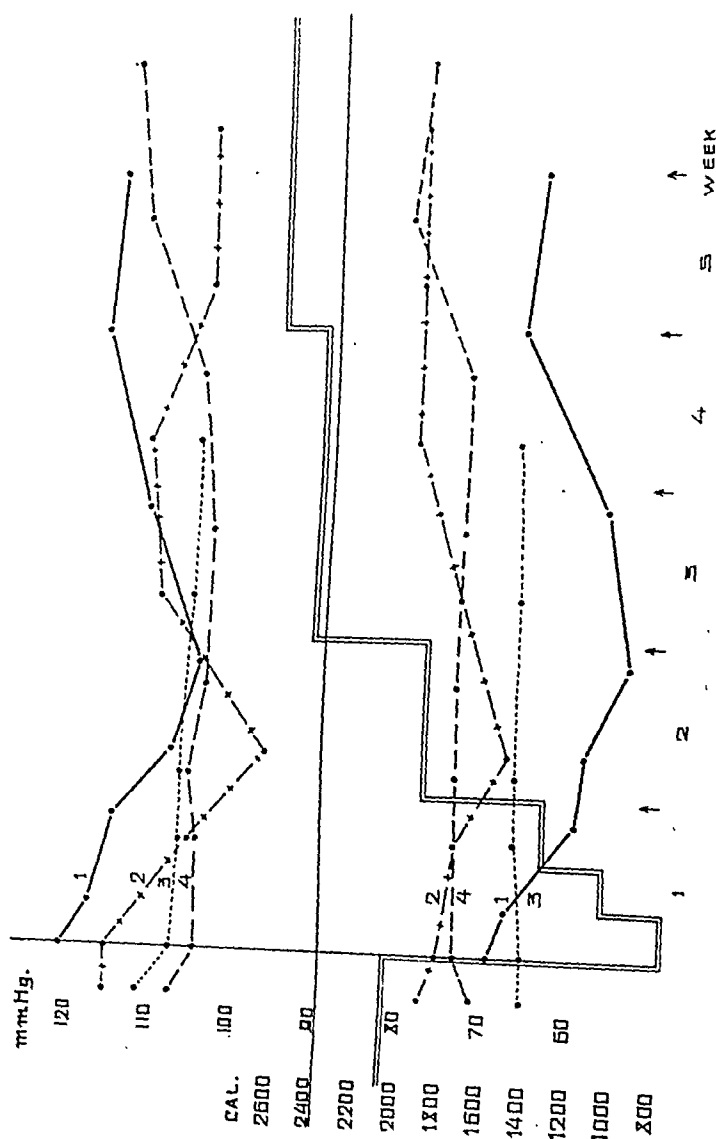
Fig. III.

Figure III indicates that two patients showed an appreciable fall in the blood pressure, which reached its minimum in the middle of the second week, just as the metabolism.

In the two other patients this fall in the blood pressure was actually absent. Patient no. 1 showed a fall of the systolic pressure of 121 to 105 mm Hg and patient no. 2 a fall of 116 to 97 mm. The diastolic blood pressure sank in no. 1 from 70 to 54 mm Hg and in no. 2 from 76 to 68 mm Hg. Why in the other two patients
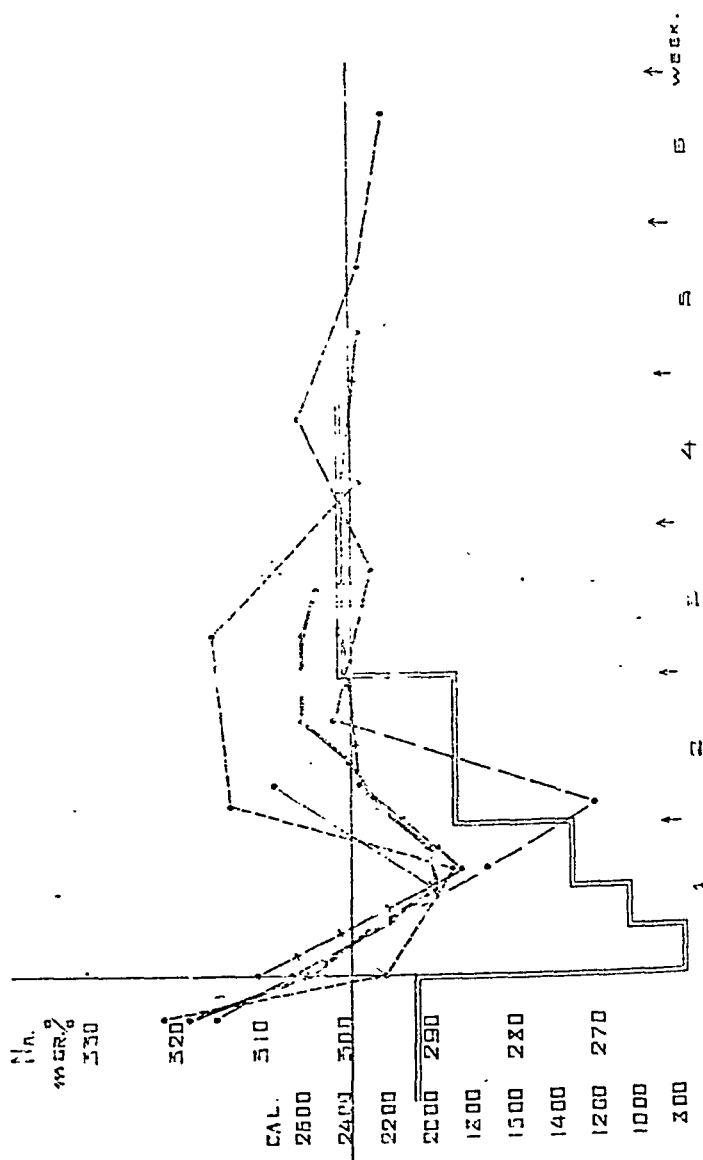
Fig. IV.

no fall manifested itself is not clear. It is possible that starvation was as yet of too short duration or that it was not drastic enough to cause a fall in the blood pressure.

Anyhow it is evident from this that starvation in all probability also lowers the metabolism of the adrenal medulla. We have

traced the influence exercised by starvation on the adrenal cortex from the action of the sodium content of the serum. To this purpose we determined the sodium content of the serum, after Butler and Tuthill, in four Sippypatients, directly after the investigations of their metabolism.

Figure IV shows the course of the sodium values in these patients. Here we see a marked fall in the percentage of sodium in the serum in the first week in all cases, invariably to under 290 mg per cent. and in one case even to 271 mg per cent. The fall in these patients reaches its lowest value already in the first week, whereas the fall of the blood pressure and of the metabolism only reaches its minimum in the middle of the second week. So the suprarenal cortex probably reacts more rapidly to starvation than the thyroid gland.

The fall in the percentage of sodium is on an average from 305 mg per cent. before the cure to 290 mg per cent. in the middle of the first week, i.e. an average fall of about 15 mg per cent. In the middle of the second week the sodium content is again normal, the suprarenal gland evidently recovers more rapidly on starvation than the other endocrin organs. We have been wondering whether this fall in the sodium content might be connected with a reduced sodium supply in the food. According to Verhagen (17) and to our own experiments, the sodium content of the serum practically does not fall in cases of a strict saltless diét and so this fall can only be ascribed to the reduced calory-supply.

Also from the pancreas one sees that starvation makes its influence felt. This is clearly shown by the course of the blood sugar curve. At the beginning of the Sippy-cure one sees a rise in the curves, which were normal before the cure. Here and there the curves resemble diabetic curves. When the nourishment is brought to its normal level this feature disappears. Fig. V.

This reduced tolerance for carbohydrates must be ascribed to the reduced activity of the pancreas, which — perhaps owing to a lack in carbohydrates — produces too little insulin, and consequently cannot cope with the excess of glucose.

Goldblatt (18), Sweeny (19), Lichtwitz (20) and others pointed out that even after a short continued fast of 36 to 48 hours, a distinct hyperglycaemie is found, when an excess of carbohydrates is given.

P. M. J. SCHWEITZER.

Figure V.

Testperson No. 1.

	bl.s. fasting	after ½ hr.	after 1 hr.	after 1 ½ hrs.	after 2 ½ hrs.
before cure	0.79	1.23	1.46	1.13	0.79
2nd day 2nd week	1.02	1.80	1.83	1.00	0.79

Testperson No 2.

	bl.s. fasting	after ½ hr.	after 1 hr.	after 1 ½ hrs.	after 2 ½ hrs.
before cure	0.89	1.27	1.30	1.03	0.74
2nd day 2nd week	0.90	1.88	1.67	1.13	0.90
1st day 3rd week	0.96	1.47	1.53	1.23	0.96

Testperson No. 3.

	bl.s. fasting	after ½ hr.	after 1 hr.	after 1 ½ hrs.	after 2 ½ hrs.
before cure	0.91	1.45	1.30	1.00	0.74
2nd day 1st week	0.74	1.14	1.78	1.82	0.93
3rd day 2nd week	0.80	1.35	1.38	1.42	0.82

Testperson No. 4.

	bl.s. fasting	after ½ hr.	after 1 hr.	after 1 ½ hrs.	after 2 ½ hrs.
before cure	not determined				
5th day 1st week	1.28	1.97	2.02	1.19	?
6th day 6th week	1.09	1.45	1.46	1.52	1.49

Testperson No. 5.

	bl.s. fasting	after ½ hr.	after 1 hr.	after 1 ½ hrs.	after 2 ½ hrs.
before cure	not determined				
3rd day 1st week	0.81	2.18	1.69	1.38	1.21
3rd day 4th week	0.92	1.35	1.36	1.19	0.85

Testperson No. 6.

	bl.s. fasting	after ½ hr.	after 1 hr.	after 1 ½ hrs.	after 2 ½ hrs.
before cure	not determined				
6th day 1st week	1.05	2.24	2.17	1.88	1.24
End 6th week	0.97	1.58	1.59	1.38	1.21

Grunwald (21) and Sweeny (19) found the same, though less notably, after diets deficient in carbohydrates or with an excess of fats.

This makes it probable that starvation reduces the activity of the pancreas metabolism with the result that the organism is no longer able to oxidize the glucose offered.

Lichtwitz (20) suggests the possibility that the liver-cells may have suffered and may no longer be able to store the glycogen rapidly enough, which might lead to a rise in the blood sugar level.

If this theory should be correct the rise in the blood sugar level on starvation, as seen in the beginning of the Sippy-cure, points to a deficiency of the liver, which in itself is not unlikely. Thus we saw that starvation which occurs in the first week of the Sippy-cure caused a reduced activity of the thyroid gland, the pancreas, the suprarenal cortex and presumably of all the endocrine organs.

At last the following question arises: how is this reduced activity brought about? Is it directly due to a reduction of foodstuffs circulating in the blood, which causes a direct under-nutrition of these organs, or is everything regulated by nerve- or hormon-centres of a higher order, e.g. by the pituitary or by the central nervous system?

One cannot make certain about this, of course. In fact we know from all kinds of investigations how susceptible the nervous tissue and cardiac muscle tissue is to an optimal sugar concentration of the surrounding tissue fluids. A fall in the sugar level, immediately causes a reduced activity of these tissues both in vivo and in vitro. So we may safely assume that the reduced activity of the endocrine organs in starvation runs parallel with a reduction of the average bloodsugar level, which has a direct influence on the cells of these organs.

The fact that the lowest fasting blood sugar values were found in the first week of the Sippy-cure is strongly in favour of this supposition. The drops were of the order of 0.10 to 0.20 per thousand but sometimes much greater. In some Sippy-patients there were in the first week fasting blood sugar values as low as 0.52 and 0.60 per thousand.

We have also tried to find out whether the serum cholesterine sinks in starvation during the Sippy-cure, but just as Master, Jaffe and Dack (9) we could find no changes in it.

· Conclusion.

In the foregoing pages we have pointed out the great importance of the calory-supply with respect to basal metabolism. In the first place we found that short-continued starvation of only a few days can appreciably influence the metabolism. This influence of starvation, however, is not restricted to a reduced activity of the thyroid gland only, but makes itself felt in the other endocrine organs as well. Furthermore attention has been drawn to the fact that the metabolism of the entire Dutch population is clearly influenced by the reduced nutrition and that the average metabolism of the whole nation has sunk by at least 6 per cent. This is accompanied by a less frequent occurrence of hyperthyroidism, which may point to a relation between excessive feeding and this disease.

All this is of great importance for the clinical investigations of the metabolism and especially for their appreciation. Here it is absolutely necessary to take into account the food taken during . the days before the investigation of metabolism and it will probably be necessary to change over in these days a nutrition with a caloric value adapted to the patients' normal metabolic rate.

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Disturbance of Circulation in Convulsions of the Epileptic Type.

V. X-ray appearance of the heart during electroshock.

By

BENGT HOLMGREN and B. P. SILFVERSKIÖLD.

(Submitted for publication June 16, 1944).

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Munson (1908) believed the disappearance of the pulse during epileptic attacks to be due to some other cause than cessation of the heart beat. By means of electrocardiography, Erickson (1939) was able to confirm this belief, his experiments being carried out not only on the pulse at the wrist, which is often difficult to study during the convulsions, but also on the pulsations in the cerebral arteries. It has further been established that the disappearance of the pulse is not to be explained by collapse, since the arterial pressure is not lowered during the attack (Erickson 1939, and other investigators).

In electroshock similar conditions can be observed by direct measurement during the violent epileptic convulsions. In these convulsions the arterial pressure rises steeply at the beginning of the attack and only drops to a low figure towards the close; the pulse waves can not be distinguished at any time during the convulsion (Silfverskiöld and Åmark 1943). The heart tones are auscultated during the last half of the tonic phase, and it is clear, therefore, that a pause in the heart beat can not be the sole explanation in these attacks either. However, since such an occurrence can happen during electroshock (Streit 1941), we must concede the possi-

bility that the disappearance of the pulse — at least in the initial stages — may in part be due to asystole.

It is generally believed that arterial contraction causes the pulse to become indistinguishable, an assumption which receives support from the high arterial pressure. Erickson (1939) maintains that the muscular spasm can result in compression of the arteries and disappearance of the pulse, a theory which may be true but remains to be proved. In earlier papers belonging to this series, however, observations have been reported indicating that, contrary to the opinion held by Erickson, a disappearance of the pulse may be largely due to a low stroke volume (4, 13, 17, 18).

During a convulsion, the stroke volume can not be studied by the ordinary methods. In the investigation to be described in this paper our object was to endeavour, by means of X-ray cinematograph records of the heart taken while the attack was in progress, to study the cardiac component as one of the causes of the disappearance of the pulse.

For the sake of comparison, the heart was also examined by X-ray cinematography during the course of Valsalva's experiment and in orthostatic arterial anemia in both of which conditions the pulse also sometimes becomes imperceptible, a feature which, in our opinion, may have the same background as the disappearance occurring in epileptic attacks.

Method. The experiments were carried out by means of indirect cineradiography — photographing on a fluorescent screen. Apparatuses for this purpose have been constructed in earlier years by Janker (1937) and Reynolds (1937). We used an apparatus of the type devised by Lysholm. It consists of a fluorescent screen (size, 24 cm. × 30 cm.) and a film camera. A black cloth hood is fitted closely from the screen to the camera, and the work can therefore be done in daylight. The hood is provided with a flap through which it is possible to fócus the apparatus, by fluoroscopy, on the part to be examined. The whole apparatus is mounted on a stand the height of which can be adjusted, and it can be rotated around both a horizontal and a vertical axis so that pictures can be taken from every angle.

The film camera is equipped with a Zeiss Biotar lens system of $f/0.85$ aperture. To prevent the films from becoming fogged, the
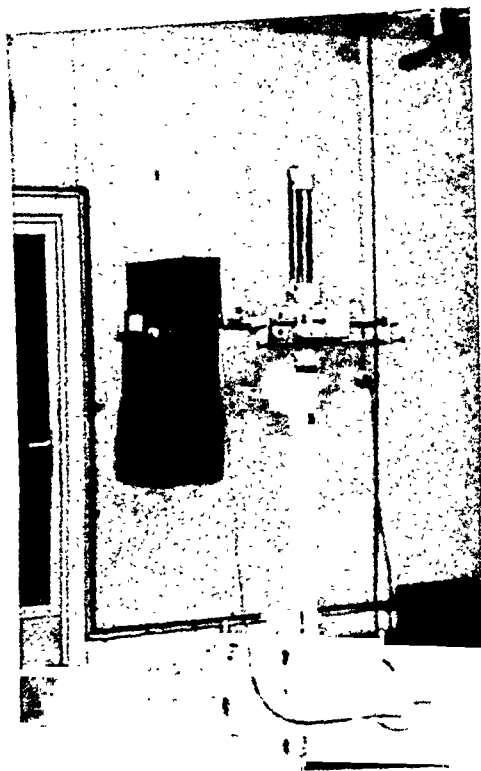
Fig. 1. The film camera.

camera is encased in lead. A 35 mm film was chosen, since it has been found by Lysholm that if narrow gauge film is used the individual pictures, even after being enlarged, are not clear enough to permit effective analysis. The apparatus is driven by an electric synchronous motor and the number of pictures that can be taken per second can be varied (4, 8, 16 and 32 pictures a second). The rate we used was 16 pictures a second. The camera is constructed in such a way that only 25 per cent of the time is »dark time».

For the examination, the patients were placed on a throcoscope table with the cineradiographic apparatus above the heart. A strap was fastened around the patient's shoulders and the upper part of his chest in order to hold him in position during the convulsion. The heart was then filmed 1) just before the start of the electroshock, 2) directly after the shock had begun, i.e. at the beginning of the tonic phase, and 3) in the middle or at the end of the clonic phase. The filming at stage 1) lasted 3 seconds and at each of the others 4 seconds.
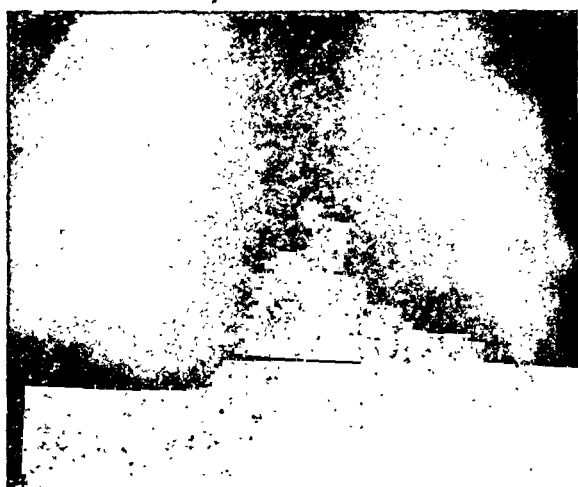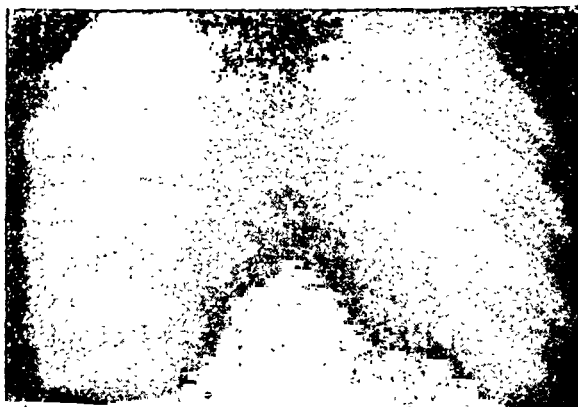
Fig. 2.   a) before the convulsion; b) at the beginning of the tonic phase;
c.) at the end of the clonic phase.

It is not possible to make exposures over the entire course of the convulsion, because the intensity of X-ray required to produce satisfactory ciné-pictures is very great. Not only is such a high load injurious to the X-ray tubes when run for some length of time, but it is also essential that the patient should not be exposed to over-irradiation. During our exposures the load on the tubes was 100 kV and 100 mA. The skin dose the patient received was 150 r.

The films we obtained were first studied one by one in a reproduction apparatus in which the picture had been enlarged on to a paper. We sketched off the outlines of the heart on this paper, and the changes in form, and enlargements and decreases in the size of the heart, could thus be studied in the frontal plane. We also, of course, projected the films on a screen in order to study the action of the heart. The latter procedure was found to give by far the better idea of both the changes in the size of the heart and the type of pulsation.

Films were taken during Valsalva experiments, in order to be able to compare the X-ray pictures of the heart with the above-mentioned pictures. The Valsalva experiments were carried out by having the subjects blow on a manometer. Exposures were made both immediately prior to the experiment, and during the blowing, after the experiment had been in progress for 25 seconds, a constant pressure of 60 mm of mercury being as far as possible maintained.

For a similar reason, we took a few films of the heart in a subject suffering from pronounced orthostatic circulatory insufficiency of the Bjure-Laurell type. Exposures were made with the subject recumbent, and then in an erect position during the insufficiency stage.

Results. We took films of the heart in seven subjects during the course of an electrically induced convulsion. It was difficult to control the patients during the exposing of the films and we only took as many as we thought would be necessary to demonstrate the essential changes in the heart action.

The films proved that there is no cessation of the heart beat. A pause might possibly have been expected to occur immediately after the electric stimulus had been given, but as the first part of the film was run directly after the stimulus and the convulsion was preceded by no noticeable latent period, a suspension in the heart

beat of any appreciable duration during the initial phase of the convulsion is out ot the question. During the second half of the tonic phase the heart tones could be auscultated. As regards the clonic phase, there is no reason to expect a stop in the pulsations; nor did our pictures show anything of the kind.

During the whole attack a moderate to strong degree of tachycardia was present.

The changes in the appearance of the heart could be clearly seen when the films were projected on a screen in the ordinary way. The individual pictures gave only a poor impression of changes in the action of the heart. Figure 2, however, shows reproductions of a picture from every stage in one of the films; thus, before the convulsion, during the first phase, and in the final stage.

The films on the whole proved very plainly that during the first part of the tonic phase the size of the heart is slightly, but nevertheless quite noticeably, diminished. The pulsations are small and rapid. This feature was observed in all seven cases.

During the middle, or at the end of the clonic phase the heart became considerably reduced in size. (The shadow of the heart in the picture is much lighter, indicating that its sagittal diameter has become smaller. this lighter appearance, however, is not visible in the pictures reproduced here.) The same feature was observed in all five cases in which successful pictures were obtained during the clonic phase.

During the clonic phase the heart beats become strangely jerky, with rapid contractions, during which the apex is drawn upward.

In connection with both Valsalvas experiment in five subjects and in the case of orthostatic circulatory insufficiency, we obtained pictures of the same type, pictures which were in complete agreement with those described by other investigators, namely, tachycardia, decrease in the size of the heart, a lighter appearance of the heart, and a change in the type of contraction. The alteration in the appearance of the heart was not more pronounced than it was during the convulsions.

Discussion. The radiographic changes already known to occur during Valsalva's experiment (Kraus 1905, Natvig 1934, Nolte 1934, 1937) and in orthostatic arterial anemia (Laurell 1936) have

been found to be connected with a powerful decrease in the stroke volume of the heart (Wezler and Knebel 1938, Laurell 1936).

According to the evidence presented in this paper the heart shows as pronounced changes during convulsions induced by electroshock as it does in the two above-mentioned conditions, and the changes are of the same type. This fact would appear to point strongly to the likelihood that a decrease in the stroke volume also occurs during convulsions of the kind under discussion.

This is the more likely in view of the fact that, from the evidence presented in the preceding investigations in this series (4, 13, 17, 18) electroshock convulsions often imply a powerful Valsalva's experiment. In all probability, the blood becomes dammed up in the extremities, and the return flow to the heart is small, with a decrease in the stroke volume as a result.

The arterial pressure remains high, however, due in part, it would seem, to an arterial contraction (and to the high abdominal pressure). It might be thought, therefore, that the disappearance of the pulse should be due mainly to the arterial contraction.

Erickson (1939) has described cases of Jacksonian epilepsy in which the pulse only became imperceptible on the side affected by the convulsions (he was fully aware of the difficulty of palpating the pulse during the convulsion). If this finding could be verified by direct measurements of the pulse oscillations after arterial puncture — and the disappearance of the pulse established as being of vasomotor origin — it would provide evidence of the greatest interest, and a proof would be supplied that the pulsations can become indistinguishable in connection with an arterial contraction. Little is known of such a possibility, although similar phenomena can perhaps occur in hemiplegia.

Working with animals, Schmiterlöw and Silfverskiöld (1943) have demonstrated that during electrically induced convulsions a rise in blood pressure occurs which is not due to the convulsions. It should be borne in mind, however, that in Valsalva's experiment also, the blood pressure rises at the same time as the stroke volume decreases and the pulse disappears. It does not seem possible to decide what is the chief cause of arterial contraction and the rise in blood pressure occurring in man during convulsions. The powerful rise in the intrathoracic and intra-abdominal pressures, however, is in all probability quite sufficient to produce the degree of arterial pressure occurring in the convulsion (see Hamilton, Woodbury, and Harper 1936.)

According to the previously-mentioned investigations of Wezler and Knebel, and of Laurell, however, the stroke volume drops by

over 50 per cent in Valsalva's experiment and in orthostatic arterial anemia. As mentioned earlier, in convulsions the change in the appearance of the heart seems quite as noticeable, and it can be said, therefore, that the cardiac component plays an essential part in causing the disappearance of the pulse.

Investigators of the Spielmeyer school consider the brain lesions observed in epileptics to be of an ischemic nature. The theory that these lesions are vascular in origin is strengthened by the feature mentioned above and known to investigators for a long time, that the radial pulse disappears during the attacks, a fact which would seem to indicate arterial contraction. Penfield (1933), by direct inspection of the cerebral blood vessels in exposed brains, during convulsions, was also able to observe both that the pulse became indistinguishable and that there were local contractions of the arteries. This observation, of course, supplied supporting evidence for the ischemic theory.

The following two investigations, however, brought forward evidence against the ischemic theory. According to Gibbs, Lennox and Gibbs (1934), the flow of venous blood from the brain increases during epileptic attacks, and according to Penfield, von Sántha and Cipriani (1939), the supply of blood to exposed areas of the brain increases during convulsions. In the opinion of the last-named authors, the lesions in the brain could not be due to a decrease in the flow of blood to the brain during the attack; they thought it conceivable, however, that the supply of blood might nevertheless be insufficient to cope with the increased oxygen requirements of brain existing during an attack.

These investigations are of great value as being direct measurements of the blood flow. It seems, however, difficult to reconcile an increased flow of blood with a disappearance of the pulse and ischemic lesions. In a powerful Valsalva experiment, it sometimes happens that the subject under examinations becomes unconscious and collapses, with small jerky movements of the legs and arms (see Bürger 1926); in other words, the behaviour observed in cerebral anemia. This, of course, does not show that a powerful Valsalva experiment increases the supply of blood to the brain. It seems rather as if the pressure causes cerebral anemia, the decrease in the minute volume also pointing in the same direction.

Seeing that, as has already been mentioned, the electroshock con-

vulsion implies a powerful Valsalva's experiment one must won-
der what the reason can be for the discrepancy in the respective
facts.

One possible explanation is that the investigations of both
Gibbs and Penfield, and their co-workers, were affected by the
intracranial pressure. In the case of the former investigation, the
high intracranial pressure existing during the attack may have
pressed out the venous blood from the brain, and in the latter the
exposing of the brain may have had as a result that the same
pressure no longer hindered the supply of arterial blood. A second
possibility is that the investigations were carried out on com-
paratively mild convulsions and that in Valsalva's experiment
there is an increase in the blood flow up to a certain limit, after
which it falls instead.

A third possibility is that in the epileptic convulsion the Val-
salva effect is over-compensated by the high arterial pressure.
But in that case, the cerebral lesions still have to be explained in
some satisfactory way.[1]

Summary.

The appearance of the heart during electroshock convulsions
has been studied by means of cineradiography.

The heart became considerably reduced in size during the con-
vulsions.

The change was as pronounced as that observed in connection
with Valsalva's experiment or in orthostatic circulatory insuffic-
iency.

It can be assumed, therefore, that the stroke volume of the heart
decreases during the convulsion.

The question of the supply of blood to the brain during the
attack is discussed.

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[1] F. Hildebrandt (Klin. Wschr. 1942, *21*, 947), studying the bloodflow
to the brain during electrochock in a dog (thermostromuhr in the internal
carotid artery), found an increase of several hundred per cent coincident
with a fall in the blood pressure amounting to 45 mm of mercury. This
is difficult to understand, especially if the intracranial pressure is high.
See also Leibel and Hall (Proc. Soc. Exp. Biol. Med. 1938, *38*, 894), who
found a diminished blood flow in the carotid artery during convulsions.

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Über Thrombozythämien mit Megakaryozytenvermehrung im Knochenmark.

Von

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(Bei der Redaktion am 28. April 1944 eingegangen).

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Während über die verschiedenen Formen der Thrombopenien und Thrombopathien ein umfangreiches Schrifttum vorliegt, finden sich nur wenige Mitteilungen, die sich mit der Überfunktion der Thrombozytopoese beschäftigen. Dabei sei die sogenannte Megakaryozytenleukose, die zuerst von Dubinskaja 1928 beschrieben wurde, hier unberücksichtigt, weil es sich dabei um Leukosen mit Riesenzellinfiltration des Knochenmarkes und der extramedullären hämopoetischen Organe handelt, deren Stellung noch nicht endgültig geklärt ist. Da hierbei eine erhebliche Leukozytose mit viel unreifen Formen besteht, kann ein Teil der beschriebenen Fälle als Leukose mit stark gelapptkernigen Myeloblasten und Promyelozyten gedeutet werden. Wir verweisen auf die in unserer Knochenmarksmonographie angeführte Literatur, besonders auf die Arbeiten von Bamforth und Kendall, Downey und Nordland, v. Boros und Korányi, Mattheus, Weil, Perlés und Scémama, Lindeboom u.a.). In diesen Fällen von Megakaryozytenleukosen wurde übrigens eine periphere Plättchenvermehrung vermisst.

Wir wollen hier über periphere Thrombozytenvermehrungen berichten, die ein erhebliches Ausmass erreichen und mit einer im Sternalpunktat nachweisbaren Hyperplasie der Megakaryozyten einhergehen. Die Thrombozythämie übertrifft dabei die infek-

tiösen Plättchenvermehrungen, wie wir sie parallel zur Leukozytose bei verschiedenen Krankheiten feststellen können. Wir unterschieden in unserer Monographie über intravitale Knochenmarksuntersuchung primäre oder *essentielle und sekundäre Thrombozythämien*. Unter ersteren verstanden wir Fälle, bei denen die Thrombozythämie und die dadurch verursachten Erscheinungen den einzigen pathologischen Befund darstellen, während bei den sekundären Thrombozythämien die Plättchenvermehrung lediglich Begleiterscheinung der bekannten Hauptkrankheit ist. Die Polyzythämie ist von diesen Krankheitsbildern zu trennen.

Über primäre, persistierende Thrombozythämie ohne Polyzythämie (in dem einen Fall bestand sogar eine Anämie von 28 % Hb und 2.8 M Erythrozyten) berichteten Rowlands und Vazey. In dem einen Fall betrug die Plättchenzahl 1, 2, in dem anderen 1.8 Million. Da es infolge der erhöhten Plättchenzahlen zu Thrombosen kam, hat die Thrombozythämie als Krankheit eine praktische Bedeutung. Bioptische Knochenmarksuntersuchungen wurden in diesen Fällen nicht vorgenommen. Uotila beschrieb einen Fall mit 5 Million Thrombozyten, bei dem er im Sternalpunktat eine Megakaryozytenvermehrung fand, wobei die Riesenzellen zunehmend pathologische Veränderungen zeigten. Reid beobachtete eine 71jährige Frau, bei der eine Leukozytose von 14,000—18,000 mit neutrophiler Linksverschiebung, eine Plättchenvermehrung von 1.73 bis 3.8 Million bei normalem rotem Blutbild feststellbar war. Im Sternalpunktat fand sich eine starke Megakaryozytenvermehrung. Merkwürdigerweise bestand trotz der erhöhten Thrombozytenzahl eine Neigung zu Haut- und Schleimhautblutungen und die Blutungszeit war auf das Dreifache der Norm verlängert (Retraktion, Gerinnungs- und Prothrombinzeit normal). Da eine verlängerte Blutungszeit in der Regel bei Plättchenmangel zu beobachten ist, könnte hier eine Funktionsuntüchtigkeit der nach der Zahl erhöhten Thrombozyten, eine Art Thrombasthenie vorgelegen haben. Nach Reid soll die Thrombozythämie eine chronische Krankheit älterer Leute mit Neigung zu Haut- und Schleimhautblutungen, Leukozytose, LV, gelegentlicher Monozytose und Eosinophilie sein, bei der im Sternalpunktat eine gesteigerte Erythro-, Leuko- und Thrombozytopoese feststellbar ist. Da dieser Markbefund mit dem der Polyzythämie identisch ist, ist es fraglich ob es sich hier um eine primäre Thrombozythämie handelt,

umso mehr, als ausser der Leukozyten- und Thrombozytenvermehrung auch eine erhöhte Erythrozytenzahl (5.05 M) gefunden wurde.

Noch unklarer ist die Zugehörigkeit des Falles von Hamaguchi und Akazaki, weil hier bei der Autopsie nicht nur im Knochenmark, sondern auch in der Leber und Milz eine erhebliche Megakaryozytenwucherung gefunden wurde, so dass an Beziehungen zur Megakaryozytenleukose zu denken ist. Der Fall von Petrescu, Olaru und Vereanu konnte diagnostisch noch weniger abgeklärt werden. Die Autoren teilen ihre Beobachtung unter dem Titel »Étude d'un cas de thrombocythaemie ou myélose mégacaryocytaire leucémique» mit, nach der mitgeteilten Krankengeschichte handelt es sich aber wahrscheinlich um eine Polyzythämie. Der 57jährige Kranke hatte anfangs 11.5 Million Erythrozyten und 12,000 Leukozyten, 3 Jahre später eine Leukozythose von 34,000 und eine Plättchenzahl von 1.4 Million, während die Polyglobulie verschwunden war (Ery. 3.2 M, Hb. 70 %). Im Sternalpunktat war die Megakaryozytenzahl mit 2 % nicht eindeutig vermehrt. Eine Sektion wurde nicht vorgenommen. Da Pat. in den letzten 3 Jahren eine Malaria hatte, die mit Chinin behandelt wurde, ist es wahrscheinlich, dass es sich hier um eine Polyzythämie mit Hyperplasie aller drei Systeme handelte, bei der es infolge der Malaria zu Splenomegalie und Anämie gekommen ist wodurch das klinische Bild verwischt wurde.

Es bleiben also nur die Fälle von Rowlands und Vazey (ohne Markbefund) sowie Uotila übrig, die einer Kritik standhalten. An Hand von 3 eigenen Beobachtungen, von denen die zweite in unserem Buch über den Morbus Besnier-Boeck-Schaumann mitgeteilt wurde, möchten wir zur Frage der Thrombozythämie Stellung nehmen. Das Krankheitsbild muss abgegrenzt werden: 1. Gegen die Megakaryozytenleukosen, 2. gegen die Polyzythämie und 3. gegen die banalen Plättchenvermehrungen bei Infekten. Zu 1.: Die den Tumoren eigene gesetzmässige Bösartigkeit und Wucherung in den extramedullären blutbildenden Organen muss fehlen. Zu 2.: Zwecks Abgrenzung gegen die Polyzythämie sollten die Fälle mit Hyperplasie aller drei Systeme nicht als Thrombozythämie angesprochen werden, auch wenn die Plättchenvermehrung erheblicher ist, als wir sie bei der Polyzythämie gewöhnlich sehen. Zu 3. ist, abgesehen von der bei Infekten oft fehlenden Megakaryozytenvermehrung im Mark, die Frage der Quantität der Thrombozyten von Belang, d.h. welche Plättchenzahl wir als über die übliche Infektreaktion hinausgehend betrachten. Wir wissen ja, dass bei keiner Zählmethode der anderen Blutzellen so grosse

zahlenmässige Unterschiede angegeben wurden, wie bei den Thrombozytenzählmethoden. Während einige Kammerzählungen über 500,000 als Normalzahlen angeben (Thomson, Lampert), gilt bei der weit verbreiteten Fonicschen Methode am fixierten Blutpräparat eine Plättchenzahl um 250,000 als normal, ebenso bei der von uns angegebenen Supravitalfärbung zu gleichzeitiger Zählung der Retikulozyten und Thrombozyten. Wenn dabei infolge Granulomerschwundes, besonders bei Thrombopenien, einzelne Hyalomere übersehen werden (übermikroskopische Beobachtungen von Wolpers), so spielt das für unsere Betrachtung keine Rolle, weil es sich ja immer um *Vergleichswerte* handelt. Wir sprechen von Thrombozythämie, wenn die Plättchenzahl um oder über das Dreifache der Norm liegt.

Zur Frage der essentiellen Thrombozythämie können wir uns hier nicht äussern, weil wir über eigene Beobachtungen nicht verfügen. In der Literatur sind nur die erwähnten 3 Beobachtungen bekannt. Über sekundäre Thrombozythämien wurde im Schrifttum überhaupt noch nicht berichtet, so dass einschlägige Fälle vom Interesse sind, umso mehr als sich das klinisch-hämatologische Bild offenbar mit dem der essentiellen Thrombozythämie deckt. Es seien daher unsere 3 Beobachtungen näher geschildert:

Fall 1. Sch. E. 45jähriger Mann erkrankte im Herbst 1936 mit Schmerzen zwischen beiden Schulterblättern und am linken Bein. Im Frühjahr 1937 wurden die Schmerzen stärker, Pat. wurde schwach, fühlte sich müde, magerte stark ab und wurde bettlägerig. Er hatte auch Schweissausbrüche. Der Arzt stellte Rheumatismus fest und verordnete Badekur, die aber erfolglos blieb. Pat. ging dann zum Nervenarzt, der nach einer Lungenröntgenaufnahme Lungentumor feststellte und Strahlentherapie verordnete. Dez. 1937 Lähmung der rechten Gesichtshälfte. Frühjahr 1938 wieder erfolglose Badekur, im Herbst 1938 wieder stärkere Lähmungserscheinungen.

Befund: Reduzierter Ernährungszustand, Blässe, Facialis- und Hypoglossusparese rechts, gesteigerte Sehnen- und Periostreflexe, keine Pyramidenzeichen. Über dem Herzen systolisches Geräusch über der Mitralis. Lungenröntgenbild: Scharfe, bogenförmig begrenzte Verschattung im linken Mediastinum. Lumbalpunktion: Liquor klar, keine Xanthochromie, Nonne-Apelt negativ, Pandy schwach positiv, Zellzahl 15/3, Druck normal. *Blutbild:* Ery. 3.9 M., Hb. = 75.6 %, F.I. = 0.95, Leuko. 6600, davon Eos. 0.5, Stabk. 3, Segment K. 86, Lympho. 8.5, Mono. 2 %. Blutsenkung 42/71 mm, *Thrombozyten 768,000.*

Sternalpunktat: Fast normale Zusammensetzung, keine Tumorzellen: Nbl. 12.5 Myelobl. 0.5, Promyeloz. 1.5, halbreife Myeloz. 1.5, reife Myeloz.

3.5, Metamyeloz. 10, Stabk. 11, Segm. 54, 5, Baso. 0.5, Eos. 0.5, Lympho.
3.5, Monobl. 0.25, Monoz. 2.75, Endothelz. 1, Megakar. 1, Plasmaz. 2.5, jg.
u. phag. Ret. Zellen 4 %. Da Pat. über Schmerzen im rechten Oberschenkel
klagte punktierte ich den rechten *Trochanter maior*. Im Punktat fanden
wir Karzinomzellverbände und Riesenzellvermehrung (histologisch bestä-
tigt). Zusammensetzung des Punktates: Makrobl. 2/3, Nbl. 26, Myelobl. 2,
Promyel. 3 2/3, halbreife Myeloz. 6 ⅓, reife Myeloz. 15 ⅓, Metamyel.
17 ⅓, Stabk. 18 ⅓, Segm. 13 2/3, eos. Myeloz. 2 ⅓, Metamyel. 1 2/3, Reife 3,
Ly. 3 ⅓, Mo. 1 ⅓, *Megakaryoz.* 5 ⅓, Plasmaz. 1, End. 2/3, Ret. Z. 5 %.

Es ergab sich also eine Thrombozythämie von 768.000 (Fonio
u. unsere Methode) im Blut und eine Megakaryozytenvermehrung
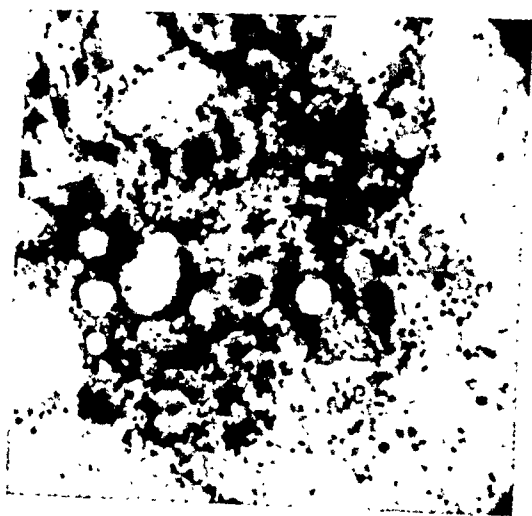
Abb. 1. Fall 1. Trochanterpunktat: Megakaryozytenvermehrung im
Knochenmark. Mikrophoto 1: 150.

im Trochanterpunktat von 5 ⅓ %. Autopsie: Bronchialkarzinom
mit Knochenmetastasen. Der Befund ist insofern interessant, als
in der Litertur bei Karzinom häufig über Thrombopenie und
hämorrhagische Diathese berichtet wurde (Kurpjuweit, Dünner,
Blum, Schildknecht), wobei im Mark normale (Blum) oder unter-
normale Megakaryozytenzahlen gefunden wurden. Eine Bezie-
hung der Riesenzellvermehrung zum Karzinom muss in unserem
Falle angenommen werden, weil sie im autoptisch metastasen-
freien Sternum nicht nachweisbar war.

Fall 2. Dieser Fall wurde in unserem Buch über den Morbus Besnier-
Boeck-Schaumann angeführt. Es handelte sich um einen 26jährigen
Bäcker, dessen Vater früher wegen Lungentuberkulose in unserer Heil-

stätte behandelt wurde. Als Kind hatte Pat. Masern, Scharlach und mit 6 ½ Jahren »Nervenentzündung«. Mit 12 Jahren »Lungenentzündung«, deshalb 8 Monate Kur in Davos. Hier auch Appendektomie. Mit 13 Jahren Tonsillektomie, mit 24 Jahren Leistenbruchoperation. Die jetzige Erkrankung begann im Januar 1940. Pat. erbrach alles was er ass und hatte eine solche Schwäche in den Beinen, dass er nicht gehen konnte. Er hatte Fieber bis 40° und fühlte sich müde. Zuerst wurde er für einen Simulanten

Abb. 2. Fall 2. Sternalpunktat: Megakaryozytenvermehrung im Knochenmark. Mikrophoto 1: 620.

gehalten, dann aber in ein Krankenhaus eingewiesen, wo er wegen vergrösserter Leber laparatomiert wurde, wobei Verwachsungen gelöst wurden. Es wurden vergrösserte Hilusdrüsen festgestellt und Pat. in unsere Heilstätte eingewiesen.

Befund: 169 cm grosser, 65 Kg schwerer Mann, pastös, sehr blass. Lungenröntgenbild: Bds. stark vergrösserte Hilusdrüsen. Tuberkulinreaktionen bis 1: 10,000 negativ, bei 1: 1000 angedeutet. Im Blutbild Anämie, normale Leukozytenzahlen und eine erhebliche Thrombozytenmehrung:

Blutbild: am 29. 5.: Ery. 3.02 M, Hb. 63 %, F. I. = 1.04, Leuko. 5,200, davon Baso. 0.5, Eos. 5.5, Stabk. 3.0, Segm. 54.0, Lympho. 28, Mono. 9 %,

Thrombozyten 875,000, Blutsenkung 60/94 mm. Leichte Poikilo-Anisozytose, Retikulozyten 10‰, Blutungszeit und Gerinnungszeit normal, Blutcalcium 11.89 mg %.

Sternalpunktat: Proerythrobl. 1 2/3, Makrobl. 6 1/3, Normobl. 40 2/3, Myelobl. 1 1/3, Promyel. 3 2/3, halbr. Myeloz. 7 2/3, reife Myeloz. 11 1/3, Metamyel. 13 1/3, Stabk. 14 1/3, Segment. 14, eos. Myeloz. 2 1/3, Metamyel. 3, Reife 1 1/3, Lympho. 5 1/3, Mono. 1, *Megakaryozyten 11 1/3*, Plasmaz. 4 1/3, jg. Ret. Z. I. phag. Ret. Z. 2/3, Endz. 2/3 %. — Es ergab. sich also eine erhebliche Riesenzellvermehrung.

Der Verlauf bestätigte unsere Diagnose »Morbus Boeck« bzw. epitheloidzellige Retikuloendotheliose (sive Granulomatose). Pat. erholte sich ausgezeichnet, die Anämie wurde behoben: Ery. 4.3, M, Hb. 89 %, das weisse Blutbild zeigte zum Schluss eine Eosinophilie von 10.5 % und die Thrombozytenzahl ging sukzessive auf normale Werte zurück, am 14. Nov. betrug sie 228,000, die Blutsenkung wurde normal (4—13 mm).

Es handelte sich hier also um einen Morbus Besnier-Boeck-Schaumann (epitheloidzellige Retikuloendotheliose sive Granulomatose) mit Anämie, normalen Leukozytenzahlen und Thrombozythämie von 875,000. Die anfänglichen leichten Lähmungserscheinungen haben wir als Symptome einer Enzephalitis bzw. Enzephalomeningitis gedeutet, wie sie bei der epitheloidzelligen Granulomatose öfters beobachtet wurde (s. Waldenström). Die plötzlichen starken Schmerzen im linken Oberbauch und das anhaltende heftige Erbrechen könnten auf einer Milzvenenthrombose beruhen, die durch die Thrombozythämie begünstigt wurde. Die Ätiologie der Thrombozythämie bleibt bei dieser Annahme allerdings unklar, während wenn man die Milzvenenthrombose nicht als Folge der Thrombozythämie ansieht, sondern als Komplikation der epitheloidzelligen Granulomatose, bei der die Milz häufig befallen wird, die Erklärung mit der splenopathischen Markwirkung offenbleibt. Man könnte an eine isolierte Enthemmung des megakaryozytopoetischen Markanteils durch eine partielle Unterfunktion der hyperplastischen Milz denken, wenngleich die Riesenzellzahl im Mark bei jeder splenopathischen Markhemmung erhöht ist. Diese Erhöhung ist aber in der Regel nicht so hochgradig.

Fall 3. L. O. 43jährige Pat., familiär nicht belastet; Pat. ist die jüngste von 10 Geschwistern. Sie leidet seit dem 7.-ten Lebensjahr an Fettsucht, die mit keiner Behandlung beeinflusst werden konnte. Mit 5 Jahren Drüsenschwellungen im Anschluss an Zahnextraktionen. Danach Unfall, Bruch des linken Armes, wonach angeblich Knochensplitter zurückblieben, so dass Pat. mehrmals operiert werden musste. Mit 12 Jahren wegen einer

tuberkulösen Coxitis 2 Jahre mit Extension und 2 weitere Jahre in Leysin behandelt. Dann 1 Jahr Solbäder. Mit 15 Jahren Augenentzündungen. Mit 40 Jahren erkrankte Pat. wieder mit Schmerzen im rechten Hüftgelenk und im Rücken. Zuerst wurde Rheumatismus, dann Wirbelsäulen- und Hüftgelenktuberkulose festgestellt, weshalb Pat. 3 ½ Jahre lang im Spital behandelt wurde. Von hier Einweisung in die Heilstätte.

Befund: Kleine (150 cm) Pat. mit enormer Adipositas, mit derben, grossen Fettwülsten, Hals zwischen dem adipösen Gesicht und Rumpf

Abb. 3. Fall 3. Endokrine Fettsucht (Surrenalismus). Gleichmässige Verteilung der Fettsucht auf Rumpf u. Extremitäten.

verschwunden. Die extreme Adipositas ist ziemlich gleichmässig auf den ganzen Körper verteilt, Rumpf, Extremitäten, Gesicht sind gleichermassen befallen. — Dunkle Komplexion, starker Bartwuchs. Achsel- und Schamhaare normal. Menses mit 13 Jahren, immer zu schwach, oft monatelange Amenorrhoe. Zähne cariös. — Lungenbefund physikalisch und röntgenologisch normal, das linke Zwerchfell ist weniger gut verschieblich als das rechte. Deutliche Druckempfindlichkeit der Wirbelsäule bei D X—D XII, kein Stauchungsschmerz. Starke Druckempfindlichkeit der rechten Hüftgegend, Bewegungen des rechten Beines unmöglich. Die Röntgenaufnahmen der Wirbelsäule zeigen Verschmälerung von D X und D XI, Verschmälerung der Zwischenwirbelscheibe, beginnende

keilförmige Verschmelzung beider Wirbel. Zwischenwirbelraum zwischen D XI und XII ebenfalls verschmälert.

Dagegen zeigt die Röntgenaufnahme der Hüftgelenke eine erhebliche Osteofibrosis mit starkem Kalkreichtum und Verbreitung der Corticalis. Es kann hier also keine Tuberkulose, sondern eine Osteopetrosis, wahrscheinlich auf endokriner Grundlage vorliegen (Abb. 4).

Wir nahmen eine Überfunktion der Nebennieren an. Dafür sprach ausser den heterosexuellen Merkmalen (Bartwuchs) auch der erhöhte

Abb. 4. Fall 3. Röntgenbild der Hüftgelenke u. Oberschenkel: Osteosklerose.

Blutdruck von 210/140 mm Hg. Ekg: Linkspositionstyp, T_4 negativ (Ableitung von der rechten Kammer). Nüchternblutzucker 98 mg %, Belastungskurve nach 50 g Glukose (oral): Anstieg maximal auf 180 mg % nach Minuten und Abfall auf 115 mg % nach 2 Stunden. Die Kurve war doppelgipfelig, der Abfall verzögert.

Blutbilder: zeigt die Tabelle 1.

Tabelle 1.

Datum	Erythroz. in Million	Hägbl. %	Leuko.	Baso. %	Eosin. %	Stabk. %	Segment. %	Lympho. %	Mono. %	Thrombo-zyten	Senkung mm
3.10.41.	4.6	94	10,700	—	5.0	3.0	75.0	13.0	9.0	610,000	24
20. 2.42.	4.68	98	8,500	—	3.0	10.0	63.0	20.0	4.0	600,000	18
4. 5.42.	5.325	96	6,650	0.5	4.0	2.5	74.5	13.0	5.5	680,000	18
3.10.42.	4.6	94	6,850	—	3.0	1.0	68.0	23.0	5.0	540,000	20
15.12.42.	5.2	94	8,050	0.5	8.0	2.5	61.0	23.0	5.0	610,000	12

Es ergab sich also immer eine erhebliche Plättchenvermehrung, während die Erythrozytenzahl normal und die Leukozytenzahl nur vorübergehend und leicht erhöht war. Das Differentialblutbild zeigte oft eine Lymphopenie und leichte LV, zum Schluss eine Eosinophilie von 8 %.

Sternalpunktat: Punktion wegen der Dicke der Corticalis schwierig. Proerythrobl. ⅓, Makrobl. 3 2/3, Normobl. 17 ⅓, Myelobl. 1, Promyeloz. 5 2/3, halbreife Myeloz. 9 2/3, reife Myeloz. 14, Metamyel. 14 ⅓, Stabk. 11 2/3, Segment. 12 ⅓, baso. Myel. 1 ⅓, Reife 1, eos. Myeloz. 5 ⅓, Metamyel. 3 ⅓, Reife 3 ⅓, Lympho. 5 2/3, Mono. 2/3, *Megakaryozyten 5 2/3*, Plasmaz. 3 2/3, jg. Ret. Z. 1 ⅓, phag. Ret. Z. 3 ⅓, Endz. ⅓, Fettz. ⅓ %. — Es ergab sich eine deutliche Megakaryozytenvermehrung bei leichter Hypoplasie der Erythropoese und LV der Granulozytopoese.

Es handelte sich also um eine isolierte Thrombozythämie bei einer Kranken mit Spondylitis, endokriner Fettsucht, Osteosklerosis der Oberschenkel und Hypertension. Trotz der Osteosklerose und Hypoplasie der Erythropoese war im Sternalpunktat eine Megakaryozytenvermehrung feststellbar. Die Klärung der Art der innersekretorischen Störung war nicht einfach. Wir nahmen eine Überfunktion der Nebennieren an, wobei sowohl die Nebennierenrinde (Fettsucht und heterosexuelle Behaarung) als auch das Nebennierenmark (Hypertension) beteiligt sind. Da die Fettsucht seit Kindheit besteht, liegt es nahe, dass primär die Nebennierenrinde befallen war und es sekundär zu einer Markbeteiligung kam (Adenom?). Die Möglichkeit, das es sich nicht um einen Hirsutismus suprarenalis, sondern um eine primäre Hypophysenaffektion mit Überfunktion des corticotropen Hormonanteils und dadurch bedingte Nebennierenhyperplasie handelt, wurde von Anfang an in Erwägung gezogen. Die Röntgenaufnahme des Schädels ergab ein normales Bild der Sella turcica. Eine hypophysäre Fettsucht anderer Art, etwa der Morbus Cushing konnte ausgeschlossen werden, weil dabei die Verteilung der Fettsucht eine andere ist (Rumpffettsucht) ferner weil dabei eine Überfunktion des Knochenmarkes mit Osteoporose (Knochenbrüchigkeit), Polyglobulie, Hyperglykämie und Hyperkalzämie besteht; alle diese Symptome fehlen aber in unserem Fall, nur die Hypertension ist gemeinsam. Die Fröhlich'sche Krankheit kommt wegen der andersartigen Fettverteilung u.a. nicht in Betracht. Eine Fettsucht infolge Dys- bzw. Hypofunktion der Keimdrüsen kann ebenfalls ausgeschlossen werden. Die Unregelmässigkeit der Menses und Hypomenorrhoe sprechen zwar für eine Beteiligung der Keimdrüsen; diese ist aber sicher

sekundär, weil die Fettsucht lange vor der Pubertät begann, ihre Verteilung eine andere sein müsste und schliesslich weil therapeutische Versuche mit massiven Dosen von Keimdrüsenhormonen (Ovocyclin Ciba, Hogival, Oestromenin u.a.) erfolglos blieben. Als fünfte Form der Fettsucht käme die cerebrale Form in Betracht, für die aber ebenfalls keine Anhaltspunkte zu finden waren.

Zwecks Sicherstellung der Diagnose wurden verschiedene Untersuchungen durchgeführt. Durch eine intravenöse Pyelographie suchte ich eine eventuelle Lageänderung der Niere durch den Nebennierentumor darzustellen. Ein einwandfreier Befund war nicht zu erheben, wenn auch das linke Nierenbecken undeutlicher als das rechte war. Die Nierenfunktion war wechselnd, Pat. hatte zeitweise viel, zeitweise wenig Urin. Ohne Einstellung zeigte der Volhard'sche Wasserversuch eine überschiessende Ausscheidung: Nach Trunk von 1 Liter Tee Ausscheidung von 1640 cm³ Urin mit einem maximalen spez. Gewicht von 1020. Bei Einstellung auf eine bestimmte Flüssigkeitszufuhr fand sich keine überschiessende Ausscheidung (1050 cm³ Urin), das spez. Gewicht betrug bei dem Konzentrationsversuch 1025. Eine Nephrosklerose konnte also ausgeschlossen werden. Auch sonst waren keine Zeichen einer Arteriosklerose feststellbar, so dass die Annahme einer endokrinen Hypertension berechtigt ist. Blutchemische Untersuchungen, die ich Herrn Doz. Dr. Schönholzer, Med. Klinik Bern verdanke, ergaben ausser einer leichten Erhöhung des Serumkaliums keine sicher pathologischen Veränderungen:

Tabelle 2.
(Mineralhaushalt von Fall 3).

	Natrium mg %	Kalium mg %	Chlor mg %	Calcium mg %	Phosphor mg %	Harnstoff mg %	Natrium: Chlor Verh.
Serum	335	25.6	363	9.7	3.2	15	1.4
Urin	235	202	314	—	—	—	1.15

Möglicherweise gewöhnte sich der Organismus im Laufe der Jahre an die innersekretorische Störung und befindet sich in bezug auf den Mineralstoffwechsel im Gleichgewicht. Auf Grund der eben angeführten Befunde erscheint uns die Diagnose der Nebennierenüberfunktion trotzdem am wahrscheinlichsten.

Wir haben hier 3 grundverschiedene Fälle vor uns, die ausser der Thrombozythämie und Megakaryozytenvermehrung nichts Gemeinsames haben. Eine Ursache der Plättchenvermehrung konnte nur im Fall 1 mit dem metastasierenden Bronchialkarzinom ermittelt werden, weil hier im metastasenfreien Sternum die Riesenzellvermehrung fehlte, während sie im mit Metastasen durchsetzten Trochanterpunktat deutlich war. Im zweiten Fall mit der epitheloidzelligen Granulomatose (Morbus Boeck) war die Ursache der Thrombozythämie nicht zu eruieren, sie führte aber wahrscheinlich zu klinischen Erscheinungen infolge einer Milzvenenthrombose. Im dritten Fall von Surrenalismus fand sich keine Beziehung der endokrinen Störung zur Plättchenvermehrung, im Gegenteil, es lag eine Osteosklerose vor, die röntgenologisch und an Hand der Dicke der Corticalis auch bei der Sternalpunktion nachgewiesen werden konnte. Im Myelogramm zeigte sich hier eine Hypoplasie der Erythropoese und Reifehemmung der Granulozyten, so dass eine isolierte Riesenzellvermehrung bestand. Im Fall 1 fand sich ebenfalls eine Hypoplasie der Erythro- und Granulozytenpoese, während im Fall 2 mit der Anämie eine leichte Hyperplasie der Erythropoese zu finden war. Da unsere Kranken den jüngeren und mittleren Altersstufen angehörten, konnte die Ansicht von Reid, dass es sich um eine Krankheit älterer Leute handelt nicht bestätigt werden. Auch die Chronizität des Verlaufes trifft für unsere Beobachtungen nicht zu. Vielleicht sind diese Charakterzüge nur der essentiellen Thrombozythämie eigen.

Zusammenfassung.

Während bei Thrombopenien zahlreiche Blut- und Knochenmarksuntersuchungen vorliegen, wurden Untersuchungen bei Überfunktion der Thrombozytopoese kaum durchgeführt. Es wird zwischen essentiellen oder primären und sekundären Thrombozythämien unterschieden, je nachdem, ob die Plättchenvermehrung den einzigen pathologischen Befund bildet oder aber eine Nebenerscheinung bei einer bekannten Grundkrankheit ist. An Hand von 3 eigenen Beobachtungen wird eine Abgrenzung des Krankheitsbildes versucht. In bezug auf das quantitative Moment wird nur dann von einer Thrombozythämie gesprochen, wenn die

Plättchen auf das Dreifache (oder mehr) der Norm vermehrt sind. Ein Polyzythämie ist klinisch und hämatologisch leicht auszuschliessen wenn man nur isolierte Thrombozytenvermehrungen berücksichtigt, ferner auch weil die Thrombozythämie reversibel ist und ohne Hypertension verläuft. Auch gegen eine sog. Megakaryozytenleukämie ist die Abgrenzung leicht, weil bei der Thrombozythämie der leukämische Umbau des Knochenmarkes und die Megakaryozytenwucherung in den extramedullären Organen fehlen; ausserdem fehlt bei der Megakaryozytenleukämie die enorme Plättchenvermehrung im Blut. Gegen die banalen infektiösen Plättchenvermehrungen ist die Abgrenzung an Hand der Plättchenzahl möglich deren Erhöhung sich hier meist in bescheideneren Grenzen hält. Ferner fehlt bei infektiösen Thrombozytenvermehrungen, wie wir uns bei vielen Infektionskrankheiten und besonders bei Tuberkulose überzeugen konnten, die Megakaryozytenvermehrung im Sternalpunktat; vielleicht liegt hier nur eine Überfunktion der Riesenzellen vor. In unseren drei Fällen konnte im Knochenmarkspunktat eine deutliche Riesenzellvermehrung nachgewiesen werden, wobei die reifen Megakaryozyten gegenüber den Megakaryoblasten überwogen. Eine Beziehung zur Grundkrankheit konnte nur in einem Fall von Bronchialkarzinom mit Knochenmarkmetastasen festgestellt werden, bei dem in der Nachbarschaft der Metastasen im Trochanterpunktat reichlich Riesenzellen zu finden waren. Bei den anderen beiden Kranken (Morbus Boeck und Surrenalismus) konnte eine solche Beziehung nicht aufgedeckt werden. Klinisch kann sich die Thrombozythämie durch Neigung zu Thrombosen bemerkbar machen, so dass sie auch eine praktisch-klinische Bedeutung hat.

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Alternating Hyperthyroidism and Myxoedema.

By

TORBEN ANDERSEN and MOGENS TRIER.

(Submitted for publication August 14, 1944).

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In The Lancet of January 16, 1943, Herman Zondek reported the case of a patient suffering from Grave's disease, who within one year, after iodine and X-ray treatment, developed myxoedema which lasted nearly four years; then, as a result of mental disturbances Grave's disease developed again and was cured under sedative treatment.

The author takes this case to support the view that hyperfunction as well as hypofunction of the thyroid must be due to factors outside this gland; neurogenic or humoral (thyrotropic hormone of the pituitary), whereas he thinks that the hypothesis about the transition from Grave's disease to myxoedema being due to temporary functional exhaustion of the thyroid has to be discarded.

This communication invites us to publish the following case which to us seems even more striking than the one reported by Zondek.

A woman, 41 years old, (Record No. 246/44) was admitted to the Medical Dep. B. of the Rigshospital the first time on 3/8/1935 and the 18th time on 11/4/44. On her first admission she presented pronounced signs of exophthalmic goiter: nervous restlessness, palpitation of the heart, tremor, loss of weight, attacks of diarrhea, loss of hair, enlargement of the thyroid, exophthalmus and tachycardia. The rate of metabolism was not increased, and this was ascribed to the preceding treatment with diiodothyrosin. On this account, treatment with iodine was continued.

The fate of this patient will be evident from the following schematic survey, which presumably will illustrate adequately the variations in the state of the patient:

Date	Treatment	Metabolism	Clinical condition
1935: 5/9	Sol. sod. iodidi 10: 300 5 cm³ × 3	105%	
6/9	» » »	102%	
18/9	» » »	107%	Hyperthyroidation
1936: 22/1	» » »	102%	
23/1	» » »	101%	
3/2	» » »	96%	
19/2	» » »	94%	
5/3	» » »	84%	Beginning hypothyroidation
20/5	» » »	85%	
22/5	» » »	81%	
24/5	No treatment		
1937: 21/6	»	84%	
22/6	»	84%	
24/6	Tabl. gland. thyr. 400 U.		
1/7	» »	100%	
7/7	» »	91%	Hypothyroidation
19/7	» »	83%	
2/12	» »	88%	
3/12	» »	86%	
4/12	» 800 U.		
1938: 30/4	» »	109%	Hyperthyroidation
2/5	» »	107%	
16/5	» »	109%	
1939: 7/6	» 400 U.		
1/7	» »	94%	
3/7	» »	93%	
4/7	» 600 U.		On the borderline of hyperthyroidation
10/7	» »	108%	
12/7	» 533 U.		
17/7	» »	94%	
1940: 26/3	No treatment		
28/3	»	124%	
1/4	»	116%	
25/5	»	114%	
27/5	»	103%	
20/6	»	112%	Hyperthyroidation
1941: 25/4	»	137%	
26/4	»	139%	
28/4	Sol. potass. iodidi 10: 300 5 cm³ × 3	116%	
3/5	» » »	92%	
8/5	» » »	84%	Gradually again hypothyroidation
12/5	» » »	87%	
3/9	» » »	87%	
4/9	» » »	79%	

Date	Treatment	Metabolism	Clinical condition
1941: 7/9	No treatment	126%	Hyperthyroidation
1942: 14/1	»	127%	
15/1		129%	
20/1	»		
27/1	Sol.potass.iodidi 10: 300 5 cm³ × 3	102%	
16/2	» » »	97%	
24/2	» » »	97%	
25/2	» » »	93%	
2/3	» » »	96%	
9/3	» » »		
12/3	Subtotal thyroidectomy (Colloid goiter with lymphoid infiltration)		
30/3	No treatment	88%	
17/6	»	85%	
18/6	»	88%	
6/10	»	76%	
7/10	»	73%	Hypothyroidation
10/10	»	80%	
11/10	Tabl. gland. thyr. 200 U.		
14/10	» »	78%	
28/10	» »	84%	
28/10	» 400 U.		
3/11	» »	90%	
10/11	» »	89%	
11/11	» 300 U.		
17/11	» »	90%	
1943: 1/4	» 400 U.		
6/6	» »	117%	Hyperthyroidation
7/6	No treatment		
15/7	»	109%	
August	»	100%	Normal
1944: 13/4	»	100%	

Comments.

As mentioned already, on her first admission to the hospital the patient presented pronounced signs of exophthalmic goiter without increase in the rate of metabolism, which at that time was attributed to the preceding treatment with diiodothyrosin. It is a striking feature, however, that during later observations, prior to the performance of thyroidectomy the patient again had symptoms

of hyperthyroidation with a rate of metabolism round 100 %. During half a year of treatment with potassium iodide there was a gradual development of pronounced symptoms of hypothyroidation, and the rate of metabolism fell to about 80 %, whereafter all treatment was discontinued. On readmission, one year later (1937), the condition of the patient was unchanged, however, and now she was treated with thyroid gland tablets in varying doses for a little more than $2^{1}/_{2}$ years. Although her metabolism under this treatment kept within the normal limit, the patient again had (for the second time) symptoms of hyperthyroidation, on which account the thyroid therapy was discontinued (in March 1940).

Now the patient received no treatment for about one year, but the symptoms of hyperthyroidism persisted, and the metabolism increased to nearly 140 %, whereafter the iodine treatment was instituted again (April 1941). Under this treatment hypothyroidation developed for the second time, with a fall in the rate of metabolism of about 80 %, and after four months the iodine treatment was again discontinued (September 1941).

Now the patient received no treatment for four months, and in this period a pronounced state of hyperthyroidism developed for the third time. As these alternating changes in her state of health were unbearable for the patient she was finally advised to submit to operative treatment.

On March 12, 1941, after preoperative iodine treatment, subtotal thyroidectomy was performed.

After the operation the patient had hypothyroidation for the fourth time and was treated with thyroid gland tablets. After a transitory overdosage, which resulted in symptoms of hyperthyroidation, the thyroid gland treatment was discontinued in June 1943, and the patient has received no treatment since. In April 1944 her metabolism was still normal.

On recapitulation of our observations in this case, our findings may be summed up as follows: A woman in the forties is suffering from pronounced symptoms of exophthalmic goiter in spite of a normal or slightly elevated rate of metabolism. Under iodine treatment the metabolism falls to absolutely pathological values, and this is accompanied by the development of symptoms of a well-characterized hypothyroidation. This phenomenon is observed

three times, as in the intermediate period — in which she receives no treatment or is treated with a thyroid preparation — she has symptoms of hyperthyroidism. After thyroidectomy she now appears to be cured.

It looks as if the »normal» state of health of this patient has been a hypothyroidism in which she has developed a morbid condition of hyperthyroidism or dysthyroidism.

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Death after Treatment with Thiourea for Hyperthyroidism.

Preliminary Experiences with Thiouracil.

By

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On January 8, 1944, a patient suffering from hyperthyroidism was admitted to our department. This patient was a women, 37 years old, wife of a laborer (Rec. No. 354/44). There was no doubt about the diagnosis. Her metabolism had been measured ambulatorily 5—6 weeks before admission and was then found to be 169 % and 179 %. Prior to her admission her physician had treated her with iodine. The metabolism had not been watched under this treatment, but after a transitory improvement, her condition had again become worse, and on admission her metabolism was 167 %. In this department she was treated with sodium iodide solution 10: 300, 10 cm³ × 3 daily, and the dose was increased gradually to sodium iodide solution 20: 300, 15 cm³ × 5. Presumably on account of the previous iodine treatment, in spite of this great dosage, the patient did not become suitable for operative treatment. The metabolism fell to about 140 %, it is true, and it kept at this level for 6—7 weeks, but her general condition was poor, and the electrocardiogram showed signs of progressive damage to the myocardium.

At this point of time I got acquainted with the works of Astwood and Himsworth (The Lancet, August 14, 1943, p. 197 and October 16, 1943, p. 465). In view of the promising results reported by these authors, on March 3, 1944, we commenced to treat the patient with thiourea, which was kindly placed at our disposal by Lovens kemiske Fabrik, Copenhagen. For 2 weeks the patient was given 1.50 g thiourea daily. Owing to our slight experience concerning the effectivity of this remedy, and because its effect was claimed not to commence until about the tenth day of treatment we continued with the same dosage of iodine as before — also because, according to Himsworth, the iodine therapy would not counteract the effect of thiourea. No favorable effect on the condition of the patient could be noticed, however. Because of elevation of the temperature, her metabolism was measured only once under this treatment (on the 4' day of treatment) when it was 146 %. Three days after the discontinuance of the treatment the metabolic rate was found to be 165 %.

Under this treatment the patient soon became nauseated, and one day she vomited once; her breath had the peculiar sweetish fetor, which seems to me to remind of boiled calsify roots. On the 3' day of treatment there was already a slight rise in temperature to 37.8°, and from the 7' day the temperature rose further, reaching 39.4° on the 11' day. As we took this rise in temperature as a sign of drug fever, the administration of thiourea was discontinued on the 10' day. On the 12' day the temperature was 38.2°. On the 13' day the patient was again given thiourea for two days, which resulted in a new rise in temperature to 40.5°. After discontinuance of this treatment on the 14' day (the patient had then received altogether 16.5 g thiourea) the temperature fell rapidly to about 38°, and on the 17' day after the institution of the treatment the morning temperature was 37.5°. On this day the patient died suddenly. In the morning she had been feeling well, while her metabolism was determined, although she was rather drowsy. In the afternoon she suddenly vomited and became cyanotic; her pulse was not palpable, and she stopped breathing within a couple of minutes.

There can be no doubt that the patient died of cardiac disease and under circumstances which, as far as I know, have not been described in exophthalmic goiter patients. Prior to the institution of the thiourea treatment, the electrocardiogram showed
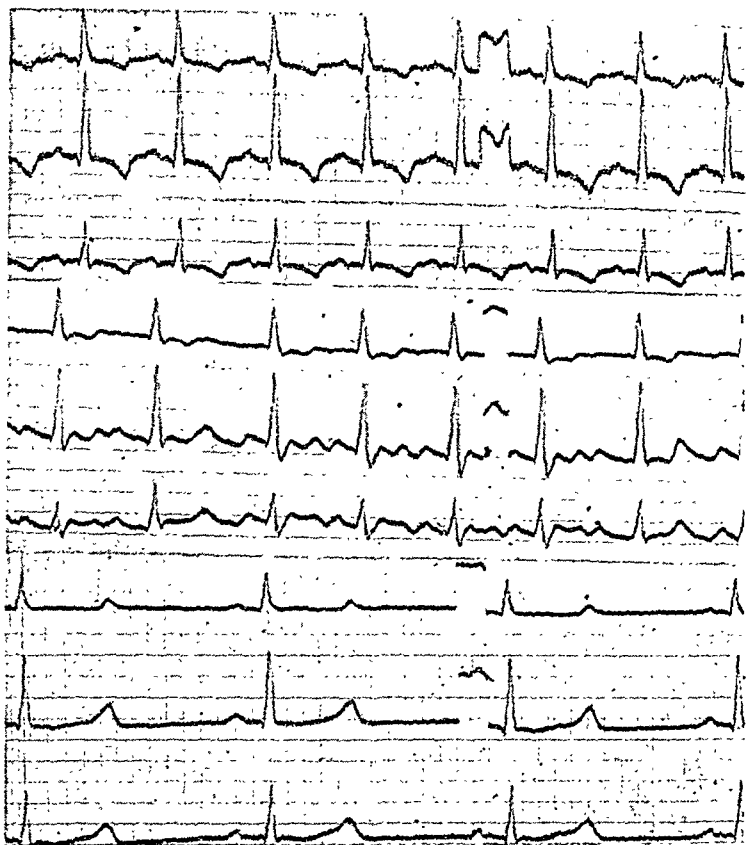
Fig. 1. Electrocardiograms taken 1) immediately before the institution of treatment; 2) 2 weeks after the institution of treatment; and 3) 3 days after the discontinuance of the treatment, on the day the patient died.

sinus rhythm with deep inversion of the T waves in all three leads. On the 14' and 16' day after the institution of this treatment the electrocardiogram showed auricular fibrillation with inverted T waves. On the 17' day after the institution of the treatment — that is, on the day the patient died — she had a slow sinus rhythm with a heart action of 40, without any preceding administration of digitalis or chinidin, and this phenomenon was checked up several times; simultaneously all the T waves had become positive and the Q-T interval was prolonged (0.580 sec. as against 0.505 sec. given by Kaj Larsen as the upper normal limit).

That the T wave turned positive may presumably be interpreted as a phenomenon secondary to the bradycardia with the resulting

improvement of the beat volume. The prolongation of the Q-T interval is not due to hypocalcemia as the serum calcium on the same day was 5.2 m.equ. As to the cause of the bradycardia, I should not venture to decide in this question. To call it the result of vagotonia would merely mean a shift of the puzzle to a new place.

Autopsy revealed enlargement of the heart and diffuse enlargement of the thyroid, which on microscopic examination presented a picture corresponding to that of exophthalmic goiter with a rather slight iodine reaction but without atypical changes of any kind. No further information was afforded by the autopsy.

At the same time we were treating another exophthalmic goiter patient — a woman, 55 years old, wife of a watchman (Rec. No. 562/44) — with thiourea. She had not been treated with iodine previously, and hence she was given no iodine now. Otherwise she received the same treatment as the preceding patient. On the 12' day of treatment her temperature commenced to rise and on the 14' day, in the evening, it reached 38.2°. On the following day this treatment was discontinued (after. the patient had received altogether 21 g thiourea), and in the following two days the temperature fell to a normal level. Under the treatment polyarthritis-like phenomena appeared in the finger, wrist, shoulder and ankle joints, and the patient had also similar dyspeptic symptoms as the preceding patient. But there were no abnormal cardiac phenomena, and the patient did not suffer any other harm. Under the treatment the metabolic rate fell from 170 % to 149 % and after the discontinuance of the thiourea therapy the decrease in the metabolism continued to 121 % without any other treatment.

The only untoward effects described so far in treatment with thiourea (apart from nausea, vomiting and sweetish fetor) are granulocytopenia and thrombopenia (Newcomb & Deane, The Lancet, February 5, 1944, p. 179). Our second patient presented none of these changes in the blood, while the first one showed a fall in the granulocyte count (71 %, 63 % and 45 %) without leucopenia, and in her case the platelet count two days before death was 145,000.

So, to the toxic by-effects of this remedy we now have to reckon also *drug fever* and *catastrophic bradycardia*.

After these poor experiences with thiourea, so far we have now treated 5 patients for exophthalmic goiter with thiouracil (Thyracil »Leo»).

Case 1.

This was the case of the above-mentioned patient who survived the treatment with thiourea. As mentioned, after the discontinuance of this treatment her metabolism fell off to 121 %. 4 weeks after the discontinuance of this treatment the patient was given thiouracil, 20 cg × 3. Under this treatment the metabolism fell of further, to 117 %, and on the 15' day after the institution of the treatment (the patient had then received altogether 1.4 g thioruracil) subtotal thyroidectomy was performed, without pre- or postoperative iodine therapy. The administration of thyracil was distontinued on the day of the operation. Postoperative course without complication. After the operation the rate of metabolism was 105%.

Case 2.

This patient (Rec. No. 543/44) showed a rise in temperature on the 9' day of treatment, increasing to 38.7° on the 11' day of treatment, whereafter the administration of thiouracil was discontinued. The patient had then received 6 g thiouracil, and in the following two days the temperature fell to a normal level. Under this treatment the patient further had leucopenia — white blood count: 5280, 3360, 2920, 2880 — but not relative granulocytopenia or definite thrombopenia. The rate of metabolism had fallen from 174 % to 130 %, however, and one week after the discontinuance of the thiouracil therapy, subtotal thyroidectomy was performed after preoperative iodine treatment. The patient was also given postoperative iodine treatment; and the course of the case was uncomplicated.

Case 3.

This patient (Rec. No. 704/44) presented arrhythmia perpetua with increasing pulse deficit on the 9' day after the institution of thiouracil therapy. This treatment was discontinued on the 17' day (after the patient had received altogether 10.2 g). Under the following iodine treatment (without any other therapy) the patient had again sinus rhythm. There was no leucopenia or thrombopenia. In this patient only a slight fall in metabolism was obtained: from 157 % to 147 %.

Case 4.

This patient (Rec. No. 855/44) showed on the 9' day after institution of thiouracil therapy a rise in temperature to 38.8° that went on to 39.7° on the 10' day, whereafter this treatment was discontinued (the patient had then received altogether 6 g thiouracil). During the following days the temperature fell to normal level. In this patient the treatment had no influence on the metabolism which kept unchanged at 160°.

Case 5.

The fifth patient (Rec. No. 783/44) showed after 12 days of thiouracil therapy (total dose of 7.2 g) without any complications, a fall in the metabolic rate from 177 % to 124 %, whereafter there was a new rise in the metabolism to 148 %. The treatment is now being continued with increasing doses of thiouracil.

In summing up these few experiences with thiouracil therapy it may safely be said that in 3 out of 5 cases we have observed a definite fall in the metabolic rate, whereas 2 cases showed only a slight effect from the treatment or none at all. *Under the treatment with thiouracil we have observed the appearance of drug fever, leucopenia and arrhythmia perpetua.* All these phenomena appeared on the 9'—10' day of treatment.

So there is every reason closely to watch these patients with a view to complications on the part of the heart and the hematopoietic organs. I think, therefore, that this treatment absolutely is unsuitable for continuous home therapy, and we are not yet so confident or feel so safe in the treatment of our exophthalmic goiter patients with thiouracil as with the old preoperative iodine treatment which has been tried out thoroughly. On the other hand, it may be that the operation on the patients showing an optimal effect from the thiouracil therapy may be carried out with greater confidence than on the patients receiving preoperative iodine treatment, as presumably the risk of the dramatic postoperative thyrotoxic crisis is avoided in the thiouracil-treated patients.

Studies on the causation of experimental gastro-prival pellagra.[1]

IV. Therapeutic Experiments on Pig with Preventive Parenteral Administration of Vitamin B_6.

By

SVEND PETRI, FLEMMING NØRGAARD and WILLIAM KIÆR.

Introduction.

In a preceding paper (1944) we have demonstrated that experimental gastroprival pellagra (= the experimental endogenous neuro-cutaneous symptom complex) in pups is influenced markedly by parenteral preventive treatment with vitamin B_6. This positive therapeutic result forms a striking contrast to all the previous therapeutic experiments carried out by us on total-gastrectomized pigs with various other vitamins B.

As the employment of pigs for our systematic therapeutic experiments is more desirable than the employment of pups, and as this now has become practicable again, we have carried out a new therapeutic experiment on this species with vitamin B_6 that will be reported in the following. The purpose of this experiment has been, partly to make possible a direct comparison with our other therapeutic experiments on pigs, partly to check up and possibly supplement the above-mentioned experiments on pups.

Material and Technique.

On account of the available amount of vitamin B_6 and with a long period of treatment desirable, this experimental study could be carried out only on one pig (No. 138). The age of the animal at the time of the operation (7—8 weeks), the performance of total gastrectomy with end-to-end anastomosis, the diet given the animal, the general experimental conditions and the blood examination have all been identical with these aspects of the previous experiments.

The observation period after the operation was 409 days; the period of treatment (instituted 2 weeks after the operation) 395 days. The vitamin B_6 preparation was the same as the one employed previously in experiments on pups (»Bayer», 1 cm³ containing 10 mg synthetic crystalline aderminhydrochloride); it was given parenterally (intramuscularly), 0.7 cm³ once a week during the first 191 days, 1.0 cm³ twice a week during the last 204 days.

The total dose of vitamin B_6 given this pig has been 76.9 cm³ = 769 mg aderminhydrochloride. Corresponding to the gain in weight of the animal, the daily dose per kg of body weight has been from 65 to 23 γ in the first period of treatment, and from 63 to 40 γ in the second period of treatment.

A non-operated and non-treated pig (No. 153) and a total-gastrectomized, non-treated pig (No. 156) have served for comparison and control.

Experimental Results.

1. *The Total-gastrectomized Pig, treated with Vitamin B_6.*

Clinical Changes. — A chronic non-fatal morbid condition developed that was characterized by rather marked inhibition of growth, moderate skin and hair changes, besides certain changes in the blood picture.

The weight was increasing gradually from 15 ½ kg to 72 kg, and the length increased from 63 cm to 105 cm. The nutrition was good, rather above middling. The skin soon became slight brownish and scaling, greasy on the back; the hair was thinning out in a rather wide, well-defined longitudinal streak on the back, extending down on the lateral surface of the hind legs; otherwise the hairs were close packed, long, curly, lusterless, and dirty yellow in color. In the latter part of the observation period the degree of the skin and hair changes was decreasing somewhat. At no point of time could clinical changes in the central nervous system be demonstrated; in particular, the posture and gait of the animal were

Fig. 1. Experimental animal: Total gastrectomized pig (No. 198), treated parenterally with vitamin B₁₂ for 305 days. Total observation period 400 days. Photographed immediately before it was killed. Length 105 cm., weight 72 kg. (age 400 days).
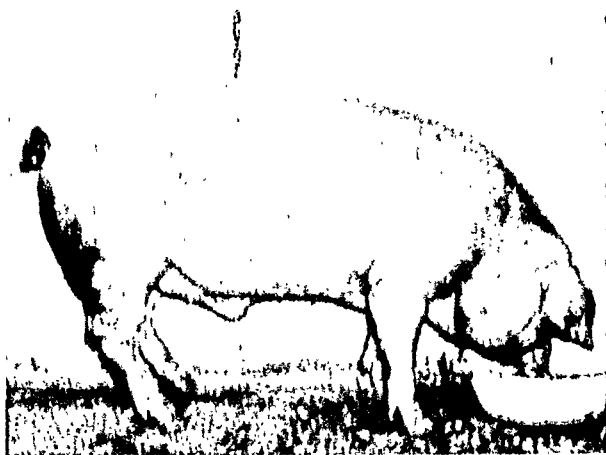
Fig. 2. Control: Normal, non-operated and untreated pig (No. 153). Photographed immediately before it was killed. Length 135 cm., weight 140 kg (age 240 days).

Fig. 3. Control: Total-gastrectomized, typically pellagrous, untreated pig (No. 156). Observation period 317 days after the operation. Photographed immediately before it died. Length 81 cm., weight 23 kg. (age 362 days).

normal. Its mental habitus was somewhat changed, the animal as a rule being cross and irritable, wanting to bite.

Changes in the blood: The hemoglobin percentage was decreasing gradually, from 71 to 41. The red blood count was constantly normal. The color index decreased from 0.64 to 0.38. The average diameter of the red blood cells decreased from 5.39 μ to 4.34 μ — owing to the appearance of more small cells (minimum 2.0 μ). In the first 6 months the white blood count varied between 11,120 and 16,240; in the latter part of the observation period it was slightly subnormal (minimum 7,000).

The appetite and defecation were normal throughout the experiment. The animal was killed by severance of the carotid artery.

Morphological Changes. — The site of the anastomosis between the oesophagus and the pyloric ring looked normal; there was no dilatation. The organs appeared normal. The spleen showed moderate infiltration with plasma cells, however, and the lymph glands and intestinal mucosa were infiltrated with eosinophil leucocytes.

Bone marrow of the vertebrae free from fat; bone marrow of the femur almost free from fat; in both places, considerable increase in the erythropoiesis. Bone marrow of the tibia: fatty marrow with slight oedema.

Central nervous system. Macroscopically and microscopically perfectly normal in all sections.

2. The Non-operated and Untreated Control Pig.

This animal developed normally and was killed at the age of 248 days. Length 135 cm.; weight 140 kg. Clinically and morphologically the animal presented perfectly normal features.

3. The Total-gastrectomized, Non-vitamin-treated, Control Pig.

Clinically and morphologically this animal developed the usual typical picture of gastroprival pellagra (see below). The animal died at the age of 362 days, with an observation period of 317 days after the operation. Length 81 cm. Weight 23 kg.

Recapitulation: A total-gastrectomized pig was given continuous preventive treatment through a period of 395 days with intramuscular injection of vitamin B_6 (altogether 769 mg adermin-

hydrochloride; daily dose per kg of body weight, min. 23 γ, max. 65 γ). Clinically some features of the gastroprival symptom complex developed: inhibition of growth, skin and hair changes, moderate isolated hypochromia, microcytosis, and erythroblastic hyperplastic bone marrow. But the central nervous system appeared normal.

Two animals served as controls: a normal pig and a total-gastrectomized, untreated pig. Conspicuous differences were found between the treated animal and, not least, the last-mentioned control (see below).

Comparison with our Previous Experimental Results.

1. In pigs, (including the above-mentioned control No. 156) total gastrectomy is followed constantly by the development of a very severe chronic and fatal illness (»experimental endogenous, gastroprival pellagra») which is characterized by: inhibition of growth (arrest of growth), symmetrical skin and hair changes, emaciation, hypochromic and microcytic anemia, clinical and morphological degenerative changes in the central nervous system, together with hyperplasia of the bone marrow [1937 (1), 1937 (2), 1938 (1), 1938 (2), 1940 (1), 1940 (2), 1941.)

From the present therapeutic experiment on the total-gastrectomized pig it is evident that preventive parenteral administration of vitamin B_6 has a pronounced effect on the gastroprival symptom complex. Thus the changes in the central nervous system, the marked emaciation and the fall in the red blood count otherwise observed in this lesion are here completely absent. The skin and hair changes together with the inhibition of growth have here been reduced in some degree. On the other hand, the fall in hemoglobin percentage, the microcytosis and the hyperplasia of the bone marrow have not been influenced by the treatment.

2. In contrast to the outcome of our previous therapeutic experiments carried out on pigs under the same conditions with vitamin B_1, lactoflavin and nicotinic acid [1938 (2), 1940 (2), 1940 (3)], vitamin B_6 is the only one of the vitamins B tried out so far that in this animal species has shown any therapeutic effect on the pellagrous symptom complex, i.e., a direct and specific effect, independent of the presence of the stomach.

3. There is considerable agreement between the result of vitamin B_6 treatment of pups for gastroprival pellagra (1944) and the outcome of the treatment of the present pig. Thus the extent and degree of the therapeutic effect on the various components of the symptom complex have been about the same in the two species. In particular, the conspicuous effect of this vitamin on the changes in the central nervous system has been further established. In the pups, however, the vitamin B_6 treatment has counteracted the skin and hair changes in a higher degree, whereas the inhibition of growth and emaciation are not counteracted to the same extent as in the pig. In the case of one of the four pups it might have been reasonable to entertain a little doubt concerning the complete effectivity of vitamin B_6 against the morphological changes in the central nervous system, but the findings in the present pig experiment appear to have invalidated this doubt.

4. The present therapeutic experiment on the pig affords additional orientation as to the size of the minimal preventive dose against the gastroprival neurocutaneous symptom complex. The dog experiments did not allow of quite definite conclusions in this respect because of the following circumstances: the difference in the therapy employed in the two groups of experiments (administration of vitamin B_6 in combination with other vitamins B or by itself alone), differences in the dosage of vitamin B_6, and the slight clinical and morphological differences observed in the action of this vitamin.

The daily doses of vitamin B_6 per kg of body weight given to the pups were on an average: min. 60 γ and max. 92 γ (given together with the other vitamins B), and min. 360 γ (later 150 γ) and max. 415 γ (later 166 γ) (given alone). As the effect of the treatment on the central nervous system has to be ascribed to vitamin B_6 alone, the preventive dose for this effect has been between 60 and 92 γ. For the other pellagrous symptoms, which are only partly amenable to the treatment, the dose of vitamin B_6 must be at least 360—415 γ. But it may also be possible that the therapeutic effect here obtained represents the maximum of the capacity of vitamin B_6 in this respect i.e., that possibly much smaller doses are just as effective.

In the present pig experiment the effect of vitamin B_6 has been identical with the most favorable effect of the vitamin therapy

in the dogs, notwithstanding that the daily dose per kg only amount-
ed to 23—65 γ. So the requirement of vitamin B_6 appears to be
smaller in the pig than in the pups. What this difference may be
due to cannot be settled here. It may be that pigs require less
vitamin B_6 than do pups, or the cause may perhaps lie in the differ-
ence in the type of operation performed on the two species (total
gastrectomy + resection of the Brunner gland area in pups, total
gastrectomy in pigs).

Summary.

A total-gastrectomized pig has been treated parenterally and
preventively with vitamin B_6 (»Bayer») throughout a period of 395
days. The daily dose per kg was min. 23 γ, max. 65 γ, and the
total dose 769 mg aderminhydrochloride. The total observation
period was 409 days.

This vitamin therapy has had a pronounced effect on several of
the components of the experimental, gastroprival, neurocutaneous
symptom complex. Particular emphasis has to be laid upon the
capacity of this vitamin for complete prevention of the degenera-
tive changes in the central nervous system.

This experiment has confirmed our experiences from similar
previous therapeutic experiments on pups. In its nature the effect
of the treatment has been the same in the two species, whereas in
degree it has been slightly deviating in some respects. The preven-
tive dose employed in the case of the total-gastrectomized pig
has been smaller than the dose required by the pups after essen-
tially the same operation.

Of the vitamins B examined so far in this way by us, vitamin
B_6 is the only one to have any therapeutic effect on the gastro-
prival neurocutaneous symptom complex (vitamins B_1, lactoflavin
and nicotinic acid were ineffective in this respect).

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Aus der I. Medizinischen Universitätsklinik Helsinki.
Vorstand: Prof. Dr. Arvo Vesa.

Studien über den Diabetes mellitus in Finnland.

III.   Das Vorkommen des Diabetes.

Von

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(Bei der Redaktion am 16 Mai 1944 eingegangen).

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Beim Untersuchen des Vorkommens der Zuckerkrankheit in Finnland haben wir uns in der Hauptsache auf zwei Fragen konzentriert, nämlich 1) Wie gross ist die Zahl der Diabetiker heute in Finnland und 2) Sind in der Anzahl der Diabetiker ähnliche Schwankungen wie in anderen Ländern nachweisbar. Die Entscheidung der ersteren Frage besitzt ausser ihrer theoretischen auch eine praktische Bedeutung. Dies geht schon daraus hervor, dass man i. J. 1942, wo infolge des Krieges zu einer Rationierung des Insulins geschritten werden musste, von Amtswegen gezwungen war, Erkundigungen über die Zahl der Zuckerkranken einzuziehen. Die Umfrage lieferte jedoch als solche keine richtige Antwort, wie wir aus folgendem ersehen werden. Indem wir anderseits die Schwankungen in der Zahl der Diabetiker untersuchen, schaffen wir eine Grundlage für die Beurteilung der Frage, wie gross die Anzahl der Diabetiker in Zukunft sein wird, und welche Bedeutung der Krankheit vom sozialen Standpunkt beizumessen ist.

Die teilweise unveröffentlichten statistischen Angaben sind uns liebenswürdigerweise vom Statistischen Zentralbüro zur Verfügung gestellt worden. Wir bitten, bei dieser Gelegenheit dem Vorstand der I. Medizinischen Universitätsklinik, Prof. Dr. Arvo Vesa, der uns das Krankengeschichtenmaterial der Klinik über-

lassen und unsere Arbeit mit wertvollen Ratschlägen geleitet hat,
unsern verbindlichsten Dank aussprechen zu dürfen.

Die *Zahl der Zuckerkranken*. Aus den amtlichen Statistiken
erhält man Aufschluss darüber, wieviel Personen in irgendeinem
Lande an Krankheiten leiden, die der Meldepflicht unterliegen.
Meistens beschränkt sich diese Pflicht jedoch auf die gemeinge-
fährlichen Infektionskrankheiten. Wenn es sich um andere Krank-
heiten handelt, muss man zu mehr oder weniger exakten Schät-
zungen, z.B. aufgrund der Sterblichkeitsstatistiken seine Zuflucht
nehmen. Beim Beurteilen der Anzahl der Diabetiker hat man auch
die während der durch die Kriegszeit bedingten Rationierung
bewilligten Lebensmittelzulagekarten als Grundlage herangezogen
(Gottstein und Umber, 1916, Kaas, 1921, Hunziker, 1922).

Im folgenden führen wir die aus dem Schrifttum zusammen-
gelesenen Angaben über die Diabetikerzahl in verschiedenen Län-
dern vor.

D e u t s c h l a n d. Im Jahre 1916 stellten Gottstein und
Umber unter Verwertung der für den Bezug von Lebensmittel-
zulagen erteilten ärztlichen Zeugnisse fest, dass die Erkrankungs-
zahl in Charlottenburg (309,000 Einwohner) 0.23 % und in Berlin
(1,800,000 Einwohner) 0.12—0.13 % betrug. Später (1939) hat
Umber berechnet, dass sich die Diabetikerzahl in ganz Deutsch-
land i.J. 1916 auf 120,000—150,000 belief, und hierbei 0.2 % als
durchschnittliche Erkrankungsziffer angenommen. Gottschalk (1931)
schätzte die Zahl der Diabetiker aufgrund der in Stettin von ihm
erhaltenen Prozentzahl (0.24) auf 150,000. Der Schätzungswert
Katschs (1934) war ungefähr ebenso gross, 120,000—150,000.
Joslin taxierte die Zahl der Diabetiker bei einem Besuch in
Deutschland i.J. 1938 auf 300,000 (Joslin, Root, White und
Marble, 1940).

D ä n e m a r k. Heiberg und Heiberg (1925) berechneten,
gestützt auf die in Leipzig gesammelten Erfahrungen, die Dia-
betikerzahl in Dänemark auf etwa 3,000. Nielsen (1928) veröffent-
lichte die Ergebnisse einer Rundfrage, die die dänische Sanitäts-
behörde (Sundhetsstyrelsen) i.J. 1927 an alle Ärzte des Landes
mit der Aufforderung gerichtet hatte, jeweils anzugeben, wie viele
Diabetiker sich an einem bestimmten Tage in der Behandlung
eines jeden befänden. Alles in allem wurden damals 4,247 Diabeti-
ker (= 0.12 %) ermittelt. Hiervon waren 2,096 Männer (darunter

471 Insulinkonsumenten) und 2,151 Frauen (429 Insulinkonsumenten) [1]. In Kopenhagen gab es 1,173 (= 0.2 %) Diabetiker, was ungefähr der von Kaas (1921) aufgrund der Krankenzulagen berechneten Zahl 1,070 entspricht. Norgaard (1932) nahm an, dass es 5—6,000 Diabetiker gäbe, von denen 2,500—3,000 Insulin gebrauchten.

In N o r w e g e n wurde die Zahl der Diabetiker i.J. 1934 auf 3,488 berechnet, von denen 1,559 (= 0.11 % der Einwohner) Männer und 1,929 (0.13 %) Frauen waren (Hanssen, 1943).

In S c h w e d e n schätzte Lundberg (1929) die Diabetiker auf 1 % der gesamten Bevölkerung oder 61,000. Diese Zahl ist im allgemeinen als zu hoch betrachtet worden (Lyon, 1932, Joslin, Dublin und Marks, 1934). Die Grundlage der Schätzung Lundbergs bildete die Diabetesmortalität, die i.J. 1925 ca 1 % der Gesamtmortalität ausmachte.

S c h w e i z. Hunziker (1922) berechnete die Diabetiker im Kanton Basel auf 0.15 %. Die Berechnung gründete sich auf die in .den Jahren 1918—1919 bewilligten Lebensmittelkarten.

E n g l a n d. Young und Russell (1926) schätzten die Zahl der Diabetiker für das Jahr 1923—1924 in England und Wales auf 24,000. Als Taxierungsgrundlage waren die in Leipzig gemachten Erfahrungen benutzt worden. Joslin, Dublin und Marks (1934) hielten die Zahl für zu niedrig und veranschlagten die wirkliche Erkrankungsziffer an Hand der Mortalitätszahlen auf 60,000.

K a n a d a. Rabinowitch (1933), der sich auf die Lebensversicherungsstatistiken stützte, hielt dafür, dass ein Diabetes bei ca 1 % der Gesamtbevölkerung vorliegt. In Kanada hätte es demnach 100,000 Diabetiker gegeben. Joslin, Dublin und Marks (1934) hielten diese Zahl indessen für unbedingt zu hoch, weil die Diabetessterblichkeit und das Durchschnittsalter der Bevölkerung in Kanada niedriger als in den Vereinigten Staaten sind. Nach ihrer Schätzung dürfte es in Kanada höchstens 30,000 Diabetiker geben.

U S A. Joslin, Dublin und Marks (1934) vermuteten, dass etwa 0.25—0.30 % der Bevölkerung oder insgesamt 250,000—400,000 Diabetiker wären. Später schätzten Joslin, Root, White und Marble (1940) die Zahl auf über 600,000 und prophezeihten, dass sie sich i.J. 1950 auf eine Million belaufen werde. Ausserdem

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[1] Dieselben Zahlen kommen in der Publikation Heibergs '1930) vor.

gab es i.J. 1940 nach ihrer Ansicht ca 2 —2.5 Mill. Einwohner, die vor ihrem Tode an Diabetes erkranken würden.

Aus Finnland sind unseres Wissens keine das ganze Land betreffenden Zahlen über die Diabetiker veröffentlicht worden.

Als Grundlage für die Beurteilung der Diabetikerzahl in Finnland haben wir die Statistik verwendet, die das Volksversorgungsministerium i.J. 1942 bei den Volksversorgungsausschüssen des Landes eingesammelt hat. Sie umfasst diejenigen Diabetiker, denen in der besagten Zeit wegen ihrer Krankheit Lebensmittelzulagen bewilligt worden waren. Die Statistik ist insofern unvollständig, als 1) ein Teil der Volksversorgungsausschüsse die Rundfrage unbeantwortet liess, und 2) in der Statistik die Angaben über viele in Selbstversorgerhaushaltungen (hauptsächlich auf dem Lande) lebende Diabetiker fehlen.

Gemäss der Statistik des Volksversorgungsministeriums gab es im Frühling des Jahres 1942 folgende Zuckerkranke:

	Männl.	Weibl.
Insulin gebrauchende	276	229
Kein Insulin gebrauchende	84	104
Diabetiker, über deren Insulingebrauch keine Angaben vorliegen	913	1,119
	1,273 (= 46.7%)	1,452 (= 53.3%)

Männliche und weibliche Diabetiker zusammen 2,725
Diabetiker, über die genauere Angaben fehlen 48

Zusammen 2,773

Um die beiden obenerwähnten Fehler in der Statistik des Volksversorgungsministeriums zu korrigieren, verfuhren wir folgendermassen:

1. Fehler. Im Gebiet derjenigen Volksversorgungsausschüsse, die die Anzeige unterlassen hatten, wohnten i.J. 1942 78 604 Einwohner, während die totale Bevölkerungsziffer des Landes 3,637,354 ausmachte. Mit Hilfe einer Gleichung erhielten wir hieraus 2 834 anstatt 2 773 als Zahl der Diabetiker.

2. Fehler. In einem grossen Teil der von den Volksversorgungsausschüssen eingesandten Antworten war auch der Beruf des Patienten vermerkt (von 1 051 männlichen und 353 weiblichen Patienten). Ihrem Beruf nach verteilten sich die Männer, um die gleiche Einteilung wie in dem Statistischen Jahrbuch für Finnland zu gebrauchen, auf folgende Gebiete:

Landwirtschaft (Ackerbau, Viehzucht, Gartenbau, Wald-
wirtschaft, Jagd und Fischerei) 174
Industrie und Handwerk 236
Verkehr 75
Handel 190
Öffentliche Tätigkeit und freie Berufe 186
Sonstige Berufe 22
Arbeiter und Tagelöhner 146
Ohne Beruf 22

Zusammen 1 051

Unter Anwendung dieser Werte auf die nach der Korrektion des 1. Feh-
lers erhaltene Diabetikerzahl ergibt sich:

Landwirtschaft .... 469 Diabetiker
Sonstige Berufe .... 2 365 »

Im ganzen Lande .... 2,834 »

Die niedrige Zahl der zum landwirtschaftlichen Beruf gehörenden
Diabetiker beruht darauf, dass ein grosser Teil der ackerbauenden Bevöl-
kerung des Landes in Selbstversorgerhaushaltungen lebt, sodass die an
Diabetes Leidenden nicht um Nahrungsmittelzulagen eingekommen sind.
Im Jahre 1930 g hörten von den 3,380,748 Einwohnern des Landes
2,014,788 dem landwirtschaftlichen Beruf an. An Hand dieses Verhält-
nisses berechneten wir die Zahl der Diabetiker, die ihren Unterhalt aus
der Landwirtschaft beziehen, erneut und kamen zu folgendem Ergebnis:

Landwirtschaft .... 3,488 Diabetiker
Sonstige Berufe .... 2,365 »

Im ganzen Lande .... 5,853 »

Diese Berechnungsweise setzt voraus, dass die Zahl der Diabetiker in
den verschiedenen Berufen die gleiche ist. Dies ist in Wirklichkeit nicht der
Fall (vgl. Joslin, Dublin und Marks, 1934). Die Zahl, die die zum Gebiet
der Landwirtschaft gehörenden Diabetiker ausweist, dürfte etwas zu hoch
gegriffen sein.

Wir können indessen wohl sagen, dass es i. J. 1942 in
Finnland etwa 5,800 Diabetiker gab, was
0.16 % von der damaligen Gesamtbevölkerung
des Landes gleichkommt (3,637,354).

Wir betrachten dann den Alters- und Geschlechtsaufbau des
Diabetespatientenmaterial Finnlands im Lichte der vom Volks-
versorgungsministerium eingesammelten Statistik.

Aus Abb. 1 erhellt die Verteilung der Diabetespatienten auf
Geschlechts- und Altersgruppen. Wir sehen, dass die Mehrheit
der Frauen in der Statistik auf der bedeutend grösseren Zahl der
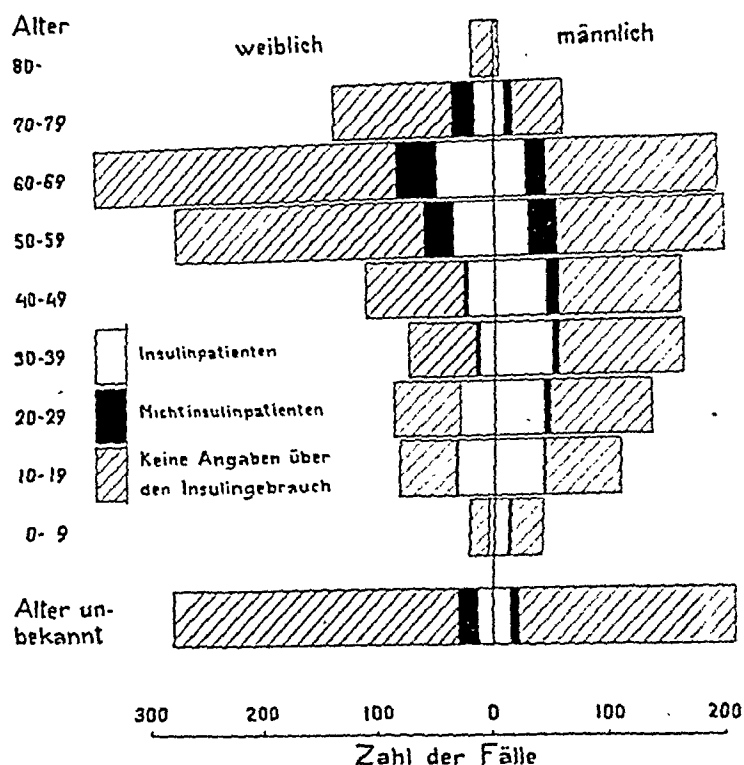
Abb. 1. Die vom Volksversorgungsministerium i.J. 1942 eingesammelte Statistik über die Diabetespatienten, die Lebensmittelzulagen hatten.

älteren, d.h. über 50-jährigen Frauen beruht. In den übrigen Jahresklassen ist die Mehrheit der Männer dominierend.

Wir wollen in diesem Zusammenhang die Statistik, die die Zahl der Diabetespatienten ausweist (Abb. 1) mit der Statistik (Abb. 2) vergleichen, aus der die Zahl der im ganzen Lande in der 3-Jahrperiode 1939—1941 an Diabetes Gestorbenen hervorgeht. Zwischen den beiden Statistiken herrscht, wie zu erwarten, eine auffallende Übereinstimmung.

Aus Abb. 1 ersieht man auch die Zahl der Insulin gebrauchenden und nichtgebrauchenden Diabetespatienten in den verschiedenen Altersgruppen. Leider fehlt in dem grössten Teil der Fälle ein Vermerk in dieser Beziehung. In den jüngeren Altersklassen scheint es relativ mehr Insulinkonsumenten zu geben, was ja auch verständlich ist.

Die Schwankungen im Vorkommen des Diabetes. Als allgemeinen Zug kann man feststellen, dass die Zuckerkrankheit in der Welt
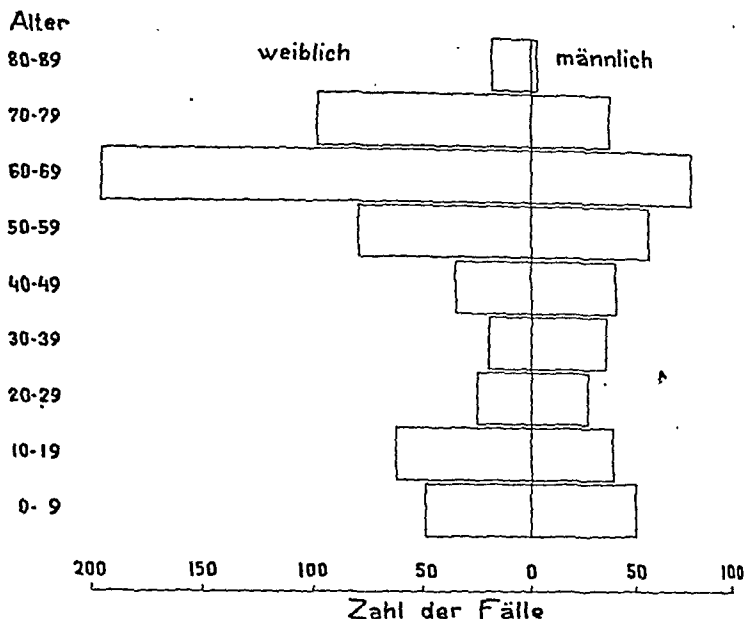
Abb. 2. Anzahl der an Diabetes Gestorbenen im ganzen Lande in der 3-Jahr-periode 1939—1941.

im Zunehmen begriffen ist. Als Todesursache stand sie in den Vereinigten Staaten i.J. 1900 an 27. Stelle, war aber bis zum Jahre 1938 auf die 9. Stelle gestiegen. Joslin und Mitarbeiter (1940) vermuten, dass sie während des folgenden Jahrzehnts die 7. Stelle erreichen wird. Die Zunahme der Diabetesmortalität ist in den alten Altersklassen am stärksten. Die Sterblichkeit der Frauen, die früher niedriger als die der Männer war, hat sich mit Ausnahme von Italien und Japan in den meisten Ländern zu der zahlenmässig wichtigeren gestaltet. Die Diabetesmortalität der Frauen ist am grössten in den mittleren und hohen Altersklassen. In den jüngeren Altersklassen steht die Mortalität der Männer nach wie vor im Vordergrunde.

Ausser den obenerwähnten haben auch viele andere Autoren eine Zunahme der Zuckerkrankheit festgestellt, so z.B. Hunziker (1922), Pirquet (1924), Ullmann (1927), Rudstein (1929), Drolet (1933), Scheel (1933), Joslin, Dublin und Marks (1934), Jagić und Fellinger (1938) und Falta (1939). Die (aus dem Anstieg der Mortalität geschlossene) Zunahme des Diabetes ist nur zum Teil eine reelle. Die Ursache für die stärkere scheinbare Zunahme bilden die

Veränderungen im Altersaufbau der Bevölkerung (Abnahme der Nativität — Zunahme der alten Altersklassen), die gegen früher vermehrte Diagnostizierung der Fälle (fortschreitende Ausbildung der Ärzte, Gruppenuntersuchungen in Schulen, Industrieeinrichtungen und zu Versicherungszwecken) sowie das verlängerte Alter der Diabetiker (Joslin, Dublin und Marks, 1935, Falta, 1939, sowie Joslin, Root, White und Marble, 1940).

Joslin (1940) zufolge ist der Diabetes in Norwegen im Abnehmen begriffen. Ebenso ist festgestellt worden, dass der Diabetes in der letzten Zeit des vorigen Weltkrieges und nach demselben (1917—1920) im allgemeinen abnahm und zwar am stärksten in den Zentralstaaten (vgl. z.B. Drolet, 1933, Lundberg, 1933, Joslin, Dublin und Marks, 1934 und Falta, 1939). Als Ursache hierfür wird die verminderte Nahrungsmenge angesehen. Möglicherweise wurde auch die Diabetesdiagnose seltener gestellt, weil die ärztlichen Kräfte an Kriegsaufgaben gebunden waren (Joslin, Dublin und Marks, 1934, Falta, 1939).

In der finnischen medizinischen Literatur finden sich einige Erwähnungen über Schwankungen in der Diabetesfrequenz, die allerdings nicht das ganze Land betreffen.

Tallqvist (1922) teilte mit, dass die Diabetesfrequenz sich in der letzten Zeit des Weltkrieges, am stärksten 1918—1919, vermindert habe. Seine Schlussfolgerungen basieren auf einem Vergleich der Zahl der in die I. Medizinische Universitätsklinik zu Helsinki aufgenommenen Diabetespatienten mit dem übrigen Patientenmaterial aus den Jahren 1912—1921. Während jener Zeit hat die jährliche Anzahl der Diabetiker zwischen 11 und 22 und die totale Patientenzahl zwischen 557 und 807 geschwankt. Um uns eine bessere Vorstellung von der Sache zu verschaffen, haben wir die Untersuchung Tallqvists nach beiden Richtungen erweitert und die relative Menge der Diabetespatienten untersucht, die in der erwähnten Klinik in den Jahren 1893—1942 behandelt worden sind. Zur Egalisierung der Prozentzahlen haben wir als Prozentsatz eines jeden Jahres den Mittelwert dreier benachbarter Prozentzahlen angenommen. Aus Abb. 3 ersehen wir das Ergebnis dieser Untersuchung. Wir bemerken, dass ausser der schon von Tallqvist dargestellten relativen Abnahme der Diabetespatienten i.J. 1918—1919 eine gleich starke Abnahme i.J. 1904—1905 festzustellen ist. Die Einführung der Insulinbehandlung hat die Diabe-

tikerfrequenz bedeutend erhöht, die aber in den dem jetzigen Kriege vorausgegangenen Jahren wieder zu sinken begonnen hat. Ausser der Einführung einer neuen Behandlungsmethode wirken auf die Aufnahme der Patienten ins Krankenhaus viele äussere Umstände ein, wie z.B., ob einer der Krankenhausärzte wegen seiner Untersuchungen usw. für die betreffende Krankheit interessiert ist. Wir sind derselben Meinung wie Falta (1939), dass man beim Ziehen von Schlussfolgerungen aus derartigen Statistiken äusserst vorsichtig sein muss.   Es sei erwähnt, dass in der entsprechenden
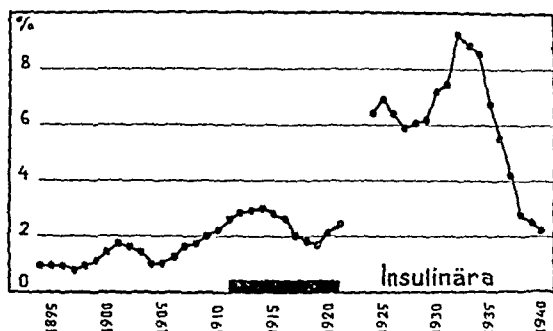
Abb. 3. Anzahl der in die I. Medizinische Universitätsklinik zu Helsinki aufgenommenen Diabetespatienten in Prozenten des gesamten Patientenmaterials. Die schwarze Linie entspricht der Untersuchung Tallqvists (1922).

Statistik Pontevas (1938) aus der II. Medizinischen Universitätsklinik, die ihr Patientenmaterial aus derselben Poliklinik bezieht, keine Abnahme in den Jahren 1918—1919 wahrzunehmen ist.

Holsti (1932) hat festgestellt, dass die Diabetessterblichkeit in Helsinki (in Prozenten der Gesamtsterblichkeit), die niedriger als in den anderen nordischen Hauptstädten ist, in der zweiten Hälfte der Periode 1911—1930 einen gewissen Anstieg aufweist.

Saltzman (1938) konstatierte, dass die Diabetesmortalität in Helsinki (im Vergleich zu der lebenden Bevölkerung), in den Jahren 1931—1935 220 % von dem ausmachte, was sie in den Jahren 1891—1895 betrug. Wir schliessen uns Saltzmans eigener Äusserung an, dass die Frequenzzunahme irgendeiner Krankheit eine nur scheinbare sein und von der verbesserten Statistik herrühren kann. Es hat wenigstens den Anschein, als ob die Angaben des i.J. 1911 gegründeten Statistischen Büros der Stadt Helsinki über die Diabetesmortalität in Helsinki zuverlässiger wären als die

Angaben der früheren Jahresberichte der Gesundheitspflegekommission.

Weil uns, abgesehen von der obenerwähnten i.J. 1942 ausgeführten Zählung der Diabetiker, keine zuverlässigen Angaben über die Anzahl der Diabetiker in Finnland zur Verfügung gestanden haben, haben wir die Schwankungen im Vorkommen des Diabetes, wie es allgemein üblich ist, im Lichte der Diabetessterblichkeit untersucht.

Wenn wir unsere Untersuchungen möglichst weit in der Zeit nach rückwärts ausdehnen wollen, verfügen wir über die Angaben, die die Lebensversicherungsgesellschaften in ihren Jahresberichten über die Todesursachen ihrer Versicherungsnehmer machen. Wir haben die in den Jahresberichten der 5 grössten Lebensversicherungsgesellschaften des Landes (Kaleva, Suomi, Salama, Pohja und Kansa, die i.J. 1942 etwa 95 % des Versicherungsbestandes sämtlicher einheimischen Lebensversicherungsgesellschaften repräsentierten) mitgeteilten Sterblichkeitsziffern der Diabetiker mit den entsprechenden Totalmortalitätsziffern verglichen.   In Abb. 4 geben wir die Ergebnisse des Vergleichs wieder.   Jeder Punkt ist dadurch erhalten worden, dass für die Zeit von 5 Jahren die Diabetestodesfälle der erwähnten Gesellschaften und anderseits die Gesamttodesfälle addiert worden sind.   Zu der die Diabetestodesfälle ausweisenden gebrochenen Linie gehört die linksseitige Skala, die die Anzahl der Fälle in 5 Jahren anzeigt, und zu der die Totalmortalität veranschaulichenden ausgezogenen Linie die rechtsseitige Skala.   Ein Vergleich der Diabetesmortalität mit der Gesamtmortalität setzt voraus, dass die auf die Gesamtmortalität einwirkenden Faktoren im Laufe der Jahre unverändert bleiben.   Dies ist natürlich nicht der Fall.   Einen grossen Fehler verursacht die Kriegsmortalität des Jahres 1918 (in den damals wirkenden 3 Gesellschaften zusammen 6,310 Fälle). Die durch diese »ausserordentliche» Ursache bedingten Todesfälle haben wir eliminiert, wodurch die die Gesamtmortalität ausweisende Kurve auch an dieser Stelle relativ gleichmässig verläuft.   Der Anstieg beruht auf der Vermehrung der Zahl der Gesellschaften und der Ausbreitung ihrer Tätigkeit.   Die Kurve der Diabetessterblichkeit wiederum scheint der Kurve der Totalsterblichkeit zu folgen.   Die Diabetesmortalität bildet infolge der verschiedenartigen Skalen, grob genommen, allem Anschein nach 1 % der Totalmortalität.
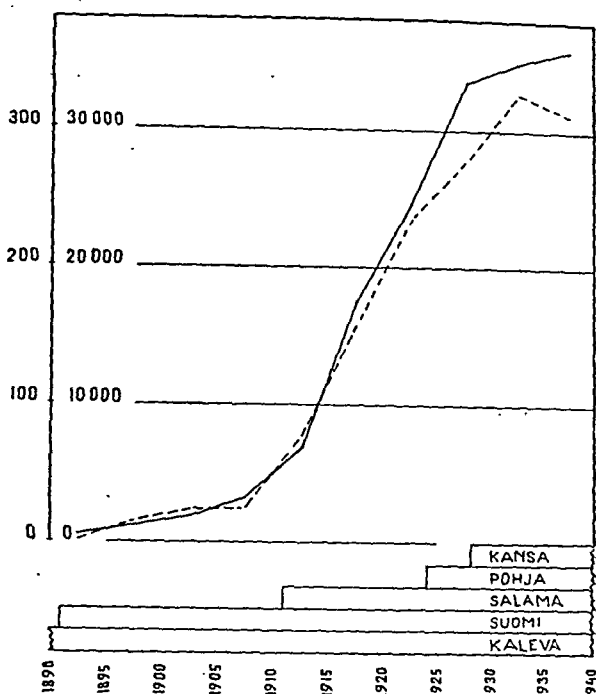
Abb. 4. Die Diabetestodesfälle der 5 grössten Lebensversicherungsgesell-
schaften Finnlands im Vergleich zu der Gesamtmortalität in den Jahren
1891—1940, in 5-Jahrperioden zusammengerechnet. *Diab tesmortalität:*
gebrochene Linie und linksseitige Skala. Gesamtmortalität: ausgezogene Linie
und rechtsseitige Skala. Zuunterst in graphischer Darstellung die Wirkungs-
zeiten der Gese schaften.

Die Mortalitätsstatistiken der Lebensversicherungsgesellschaf-
ten lassen also keine erheblichen Schwankungen der Diabetesfre-
quenz in Finnland erkennen.

Eine zweite und genauere Möglichkeit, die Schwankungen der
Zuckerkrankheit in Finnland zu untersuchen, ist die von dem Sta-
tistischen Zentralbüro eingesammelte Statistik über die Todes-
ursachen im Lande. Wir haben die Statistiken vom Jahre 1927 ab
herangezogen. In den Jahren 1927—1935 sind die Angaben auf-
grund der von den Registerbehörden herausgegebenen Todes-
anzeigen eingesammelt worden, vom Jahre 1936 ab vorwiegend
aufgrund der von den Ärzten ausgestellten Totenscheine.

In Abb. 5 stellen wir die Zahl der an Diabetes im ganzen Lande
Gestorbenen, Männer und Frauen getrennt in 3-Jahrperioden zu-
sammengerechnet, dar. Die Gesamtmenge der Diabetestodesfälle

ist dauernd gewachsen. In den drei letzten Perioden scheint die Zunahme ausschliesslich auf den Anteil der Frauen zu entfallen.

Aus Abb. 6 ersieht man die Diabetesmortalität auf Altersgruppen verteilt. Die Verteilung der Männer auf die Altersgruppen ist in den obenerwähnten 3-Jahrperioden ziemlich konstant. Ein schwaches Maximum scheint sich bei den jüngsten Jahrzehn-
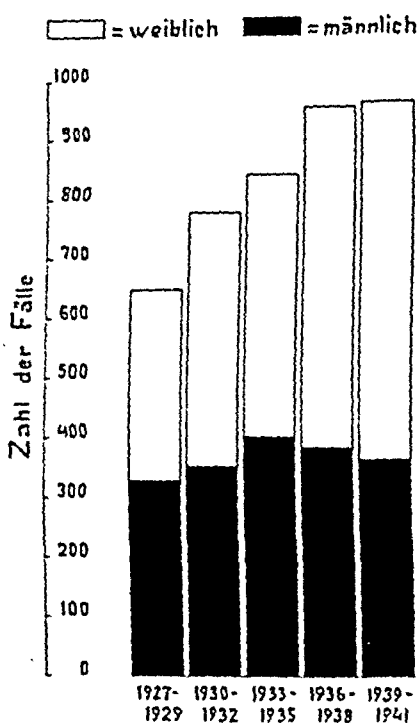
Abb. 5. Anzahl der an Diabetes im ganzen Lande Gestorbenen in 3-Jahrperioden zusammengerechnet.

ten und dem Jahrzehnt 60—69 zu bilden. In der Gruppe der Frauen dagegen, wo die beiden Maxima ebenfalls zu beobachten sind, weist das letztere Maximum von einer 3-Jahrperiode zur andern einen immer stärkeren Anstieg auf. Die Zunahme der Diabetesmortalität der Frauen beruht also in der Hauptsache auf dem kontinuierlichen ziemlich starken Anstieg der Diabetesmortalität bei den 60—69-jährigen und in den beiden daran angrenzenden Altersklassen. Dies ist auch die Hauptursache für die in Abb. 5 dargestellte Zunahme der Gesamtmortalität der Diabetiker.

Hierauf untersuchten wir, ob in der Verteilung der Bevölkerungsziffer Finnlands auf die Altersgruppen in den erwähnten
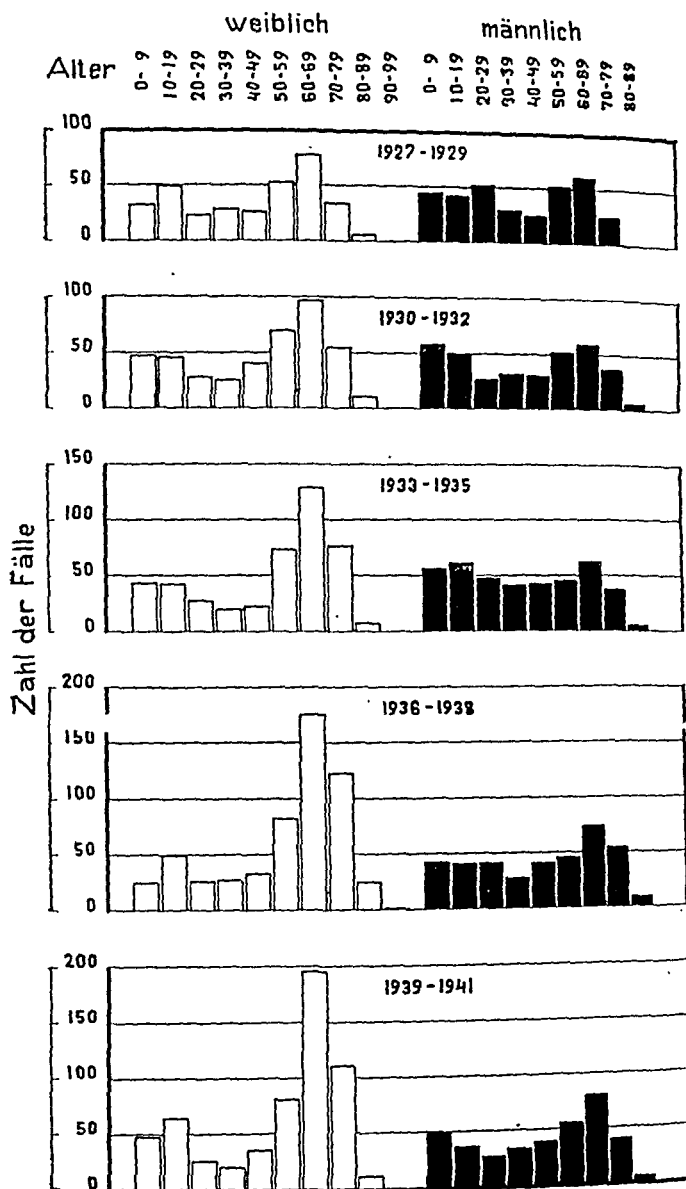
Abb. 6. Anzahl der an Diabetes im ganzen Lande Gestorbenen, nach Alters-
gruppen in 3-Jahrperioden zusammengerechnet.

3-Jahrperioden solche Schwankungen vorgelegen hätten, die mög-
licherweise die oben erörterten Veränderungen in der Diabetes-
sterblichkeit hervorrufen konnten. Aus Abb. 7 ersehen wir die
Bevölkerungsziffer Finnlands, nach Alter und Geschlecht verteilt,
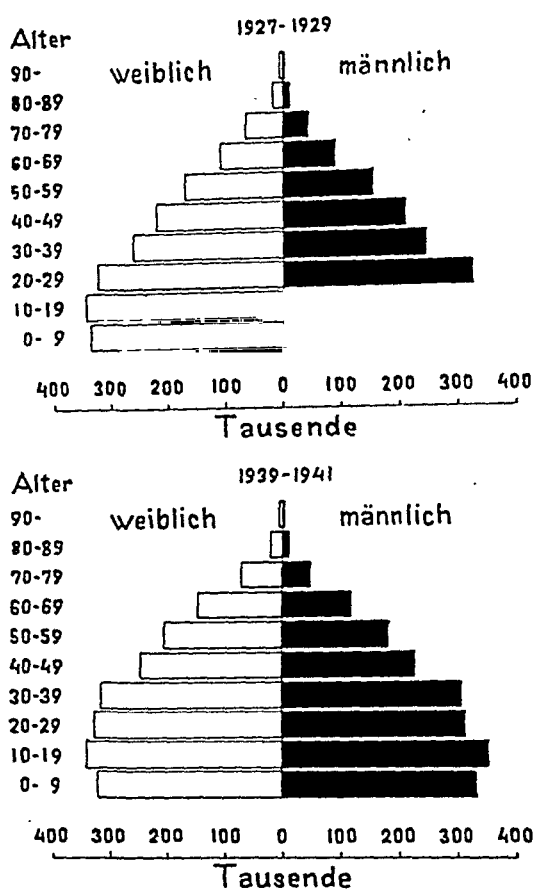
Abb. 7. Die Bevölkerungsziffer Finnlands, nach Alter und Geschlecht verteilt, in den 3-Jahrperioden 1927—1929 und 1939—1941.

in den 3-Jahrperioden 1927—1929 und 1939—1941. Beide Figuren sehen, praktisch betrachtet, gleich aus. Die die Perioden 1930—1932, 1933—1935 und 1936—1938 darstellenden Figuren, die sehr ähnlich waren, haben wir der Kürze halber fortgelassen. Für die Erhöhung der Diabetessterblichkeit bei den alten Frauen haben wir also in den Schwankungen der Bevölkerungsziffer keine Ursache gefunden.

Zusammenfassung.

Aufgrund der zwecks Lebensmittelzulagen ausgestellten ärztlichen Zeugnisse wurde berechnet, dass es in Finnland im Frühjahr 1942 etwa 5,800 Diabetiker gab, was 0.16 % von der damaligen Gesamtbevölkerung des Landes gleichkommt. Hiervon waren

46.7 % Männer. Von der Gesamtbevölkerung des Landes machen die Männer 47.6 % aus.

In den Jahren 1927—1941 hat die Diabetessterblichkeit in Finnland einen Anstieg erfahren. Derselbe hat während der letzten 9 Jahre auf einer Zunahme der Diabetessterblichkeit der Frauen beruht, weil die betr. Mortalität der Männer während dieser Periode gesunken ist.

Die Zunahme der Diabetesmortalität der Frauen ist auf die Jahresklassen 50—79 Jahre zurückzuführen, in deren mittelster (bei den 60—69-jährigen) der Anstieg der Diabetesmortalität besonders kräftig ist.

Im Alters- und Geschlechtsaufbau der Bevölkerung Finnlands haben in den Jahren 1927—1941 keine Veränderungen stattgefunden, die zu einer Vermehrung der Diabetessterblichkeit der alten Frauen Veranlassung gäben.

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Benzene Poisoning.

I. Clinical considerations.

By

CARL-OLOF OLDFELT.

The first description of benzene poisoning in man was published in 1897 by C. G. Santesson. Since that time, many reports have appeared on the effects of benzene both on animals and in human beings. In Sweden, J. Helmer has recently made a report on about 60 cases of benzene poisoning. Comprehensive reviews of the literature by Hamilton (1931), von Oettingen (1940), G. Bauer (1940), and T. Stenstam (1942) are also available.

As with all other volatile organic solvents, benzene, when inhaled in fairly high concentrations, produces a state of acute poisoning for a short period. The syndrome has been described by both Winslow (1927) and von Oettingen (1940), as well as by other workers, and it is also mentioned in the Public Health Reports for 1941 (vol. 56). The symptoms are the same as those occurring after inhalation of a narcotic. The acute form of benzene poisoning is seldom serious. As a rule there is dizziness which passes off rapidly when the subject is removed from the influence of the benzene vapors.

In its chronic form, the poisoning causes subjective symptoms which show considerable variations and have few characteristic features. They are specified in the publications by von Oettingen and by Bauer mentioned in the preceding paragraph, and also in the Public Health Reports for 1941 (vol. 56), and are set forth in

some detail in an article by Davis (1940). In some proved and fairly far-advanced cases there have even been no symptoms at all. In most instances the patient complains of fatigue, headache, vertigo, insomnia, and an unpleasant taste in the mouth.

Chronic benzene poisoning causes signs of disturbances in the bone marrow, and the objective investigation therefore concerns itself mainly with examination of the blood. Anemia, leukopenia, and thrombopenia may be present, but pictures of a polycythemic and leukemic nature have also been observed. Hemorrhages from the skin and mucous membranes may also occur. The hemorrhage or the bleeding tendency do not go hand-in-hand with the thrombopenia. If the poisoning has been allowed to continue for a long period serious illness may occur and may even prove fatal, death being due to advanced anemia or to leukopenia.

The disturbances in the blood observed in chronic benzene poisoning consist, in the large majority of cases, of anemia, leukopenia, or thrombopenia. All three of these conditions may be present at once, but they more often occur either in twos, apparently according to no particular rule, or one at a time. Blood pictures resembling polycythemia and leukemia are uncommon occurrences.

In the more advanced cases, the anemia is of the aplastic type. Macrocytosis is sometimes present (Goldwater), and Greenberg, Mayers, Goldwater, and Smith, for example, maintain that an increase in the mean corpuscular volume is a sign of incipient benzolism. (Incidentally, the author would like to point out that the mean corpuscular volume $\left(= \dfrac{\text{hematocrite} \times 10}{\text{million reds per mm}^3}\right)$ must be difficult to determine with any degree of exactitude, particularly in view of the lack of accuracy with which the numbers of red blood cells are measured. The limits stated for the normal values are in all probability too narrow (80—90 μ^3). Anemia is believed by some workers (von Jagic and Khaum) to be the commonest sign of chronic benzene poisoning. Hunter states that a rise in the number of red blood cells and the hemoglobin content above the normal values can occur.

Leukopenia has been believed for a long time to be the blood change most commonly occurring in the chronic form of the poisoning (Selling), and this belief seems to tally with the observations of most of the more recent investigators. It has often been asserted

that the granulocytes disappear to a greater extent than the lympho-
cytes; in other words, that a relative form of lymphocytosis is
present. This statement has been based on the comparatively low
percentage values stated as normal for the lymphocytes (25—35
per cent) in the current textbooks. Investigations carried out by
Osgood (1935) and by Osgood et al. (1939) have proved, however,
that the lymphocyte values can normally reach a much higher level
—up to 60 per cent. Greenberg and his co-workers (1939), and Gold-
water (1941) compared the blood values in their patients who had
been exposed to benzene with a normal series of the same age and
social status examined at the same time, and found no relative
lymphocytosis. In all probability, there is no relative lymphocytosis
in chronic benzene poisoning. An abnormal degree of eosinophilia is
also said to occur in this type of poisoning (cf. Hunter), over 3 per
cent of eosinophils being regarded as a pathologic value. The
studies by Osgood on normal material, mentioned earlier, demon-
strated, however, that an eosinophilic leukocyte count of up to 6
per cent may occur in normal blood, and Greenberg et al. (1939)
and Goldwater (1941) did not find that eosinophilia occurred more
frequently or to a higher degree than in their normal subjects. It
seems extremely doubtful, therefore, whether eosinophilia really
does constitute a feature of the blood picture in poisoning following
benzene exposure.

A decrease in the number of thrombocytes occurs in connection
with benzolism, and this is sometimes the only evidence of the con-
dition. That thrombopenia should be the only sign of the poisoning
in as many cases as is asserted by Nikulina and Titowa (1934),
however, can hardly be said to tally with the experience of most
investigators.

There has been much discussion regarding both the blood
changes which may be considered an early danger signal (Nikulina
and Titowa, 1934; Greenberg et al., 1939; Hunter, 1941), and the
investigations of value as a routine measure for discovering the
largest number of people affected after operations in dangerous
concentrations of benzene. Considering the variations observed in
the blood picture in benzene poisoning, and the diversity of the nor-
mal blood values, and not the least in view of the want of accuracy
in our hematologic methods, one can venture to say that in routine
examinations of personnel working with benzene one should make

only red and white cell counts, platelet counts, and hemoglobin estimations.

During 1943 I had an opportunity to examine and make follow-up studies on members of the personnel in the rotogravure printing industry who had been conducting operations with benzene. The results of this investigation will be described in the present paper.

The material comprises 180 persons who had been exposed to benzene. Of these, 38 were found to be suffering from chronic benzene poisoning. As regards 61 of the others, signs of acute poisoning were mentioned in the anamnesis. No objective signs of benzene poisoning were detected in the remaining 81 cases.

The normal hematologic data are indicated slightly differently by different authors. Enghoff (1937), in a Swedish series, determined the oxygen capacity in the blood to be 20.5 per cent by volume, with a standard deviation of 1.38, in men, and 17.9 per cent by volume, with a standard deviation of 1.49, in women. For clinical purposes, $M \pm 2\sigma$ is often given as the normal range of variability (cf. Osgood, 1935, and Osgood et al., 1939). Thus, the normal variability of the oxygen capacity in Enghoff's material would be 23.6—17.7 per cent by vol. for men and 20.9—14.9 per cent by vol. for women. Calculated in grams of hemoglobin per 100 cm³ of blood these oxygen capacity values give 17.5—13.4 for men and 15.6—11.1 for women. Corresponding figures according to Osgood (1935) are 18.0—14.0 g for men and 16.0—11.5 g for women. The number of red cells, in millions per mm³, is stated by Enghoff as 5.2, with a standard deviation of 0.36, for men, and 4.7, with a standard deviation of 0.33, for women. If the normal range is calculated in the same way as was done for the hemoglobin ($M \pm 2\sigma$) the values 5.9—4.5 are obtained for men, and 5.4—4.0 for women, in millions per mm³. Osgood's (1935) corresponding values are 6.2—4.6 for men and 5.4—4.2 for women. Nordenson (1940) gives the borderline values for men as 5.2—4.3 and for women as 4.6—3.9, in millions per mm³. The number of white blood cells per mm³ is stated by Osgood (1935) to be normally 7,400 with a normal range of 4,000—11,000; Osgood and his co-workers (1939) place the mean value in persons over 19 years of age at 7,400 and the normal range at 4,500—11,500. Nordenson (1940) considers that the normal limits for white blood cells lie between 4,000 and 9,000 per mm³. In the differential count the lymphocytes vary in normal blood between 18 and 65 per cent and the mean value is 38 per cent, according to Osgood et al. (1939). The same authors maintain that eosinophilia is in question only when the value goes over 6 per cent. A decrease in the normal number of platelets is thought to exist only when the platelet values drop below 100,000 per mm³. (Nordenson, 1940.)

When deciding whether the values were normal or abnormally low in each case I went by the lowest of the above-mentioned normal limits. Thus, in men, I took 13 g per 100 cm³ of blood as the lowest normal figure

for the hemoglobin content, and 4.3 million per mm^3 as the lower borderline for red cells. As regards the white cells and the platelets I used the figures 4,000 and 100,000 respectively, per mm^3. In the differential blood count I accepted the values for lymphocytes and polymorphonuclear eosinophile leukocytes mentioned by Osgood in 1935.

The usual hematologic methods were used for the estimations. The Ellerman system was applied when drawing the samples. The hemoglobin values were measured with a Zeiss hemoglobinometer which had been standardized against blood with a known oxygen capacity. For details regarding the accuracy of the hematologic methods the reader is referred to the publication of P. Plum (1936). With the methods used in our laboratory the hemoglobin determination was found to give an accuracy of ± 2 per cent. In the red cell counts about 200—250 cells were counted, and in the estimations of the white cells between 250 and 50 cells. For the differential blood count 200 cells were studied. The platelets were counted according to the Kristensson method.

A diagnosis of chronic benzene poisoning (in these personnel members exposed to benzene vapors) was made when the blood picture showed definite leukopenia or thrombopenia. If the values were only slightly below normal I made it a condition that low values should be repeatedly observed in different samples. When leukopenia or thrombopenia were combined either with one another or with anemia it was not difficult to make the diagnosis. The most puzzling cases, owing to the difficulty of excluding other likely causes, were those in which anemia was the only abnormal feature.

It should perhaps be mentioned here that in making the diagnosis chronic benzene poisoning I went solely by the objective blood findings. In a number of cases there were manifestations from the skin — eczema. These were not examined by a dermatologist, however, and no skin tests were made. There is thus no proof that they were benzene effects, and I have not included them among the signs of benzene poisoning. The significance to be attributed to the subjective symptoms for the diagnosis is as yet not clear, and I did not allow them to influence my decision.

As already mentioned, 38 of the persons examined showed signs of chronic benzene poisoning. Details regarding the individual cases will be found in the case reports at the end of this paper. The cases have been numbered 1—38. Of the remaining cases there were symptoms of acute poisoning in the past history in 61 instances while in 81 there had been neither symptoms of acute intoxication

nor evidence in the blood of the chronic condition. Only a male staff was employed at the industrial concern at which my investigation was carried out.

The age distribution is presented in summarized form in table 1.

Table 1.

Age	Cases of chronic poisoning	Others	Total
years	no.	no.	no.
<20	1	9	10
21—30	5	46	51
31—40	17	60	77
41—50	11	23	34
51—60	3	3	6
>60	1	1	2

The length of time spent at the present occupation is shown in table 2.

Table 2.

Employment time	Cases of chronic poisoning	Others	Total
years	no.	no.	no.
<1	1	29	30
1—3.9	10	32	42
>3.9	27	67	94
Not known	—	—	14

The length of time the patients had been exposed to benzene vapors is not known with certainty. A few of the workmen examined had been employed in the rubber industry, and the majority in rotogravure printing works. As a rule, a mixture of toluene, xylene, and benzine had been used as a solvent and diluent for the paint, in the rotogravure industry. It is not known whether this mixture was benzene-free, or if not, how much benzene it contained. During the years 1940—1943, the use of benzene had to be increased in Sweden, owing to the shortage of xylene and toluene. I do not know, however, when and to what extent benzene was substituted for xylene and toluene in the different industries. I took as a basis

Table 3.

Nature of disturbance in blood	No. of times encountered
Anemia + leukopenia + thrombopenia	10
Anemia + leukopenia.'.......................	12
Anemia + thrombopenia	1
Anemia (alone)	2
Leukopenia (alone)	13
Leukopenia + thrombopenia	—
Thrombopenia (alone)	—
Total	38

for my studies the assumption that benzene exposures became intensified during 1940. This state of affairs continued until the autumn of 1943, when, in consequence of the cases of poisoning occurring, the working conditions at the factories were improved, and in addition to this xylene was made available in larger quantities. The group of workers employed for four years or longer had thus been subjected to the effects of benzene for about three years, and besides this the men employed more than four years had also been engaged on the same work at the time when the mixtures of toluene, xylene, and benzine were being used. As I mentioned before, it is not known whether this mixture was benzene-free or not. If the time of employment was shorter than four years the exposure time and the employment time coincided in most cases. It will be seen from table 2 that about onefourth to one-fifth of those who were exposed to the vapors for a longer time than one year showed evidence of chronic poisoning, in this material. The degree of benzene exposure varied considerably according to the different types of operations, and also to the sensitivity in the individual cases. No mean value for the degree of benzene exposure can be given. Only in one instance (case 2) was the duration of the exposure shorter than one year.

The different types of blood changes were distributed in the manner shown in table 3.

In this series, anemia was encountered in 25 of the cases, leukopenia in 35, and thrombopenia in 11.

A differential blood count was made at least once on each pati-

Table 4.

Lymphocytes	Cases of chronic poisoning	Total
%	no.	no.
10—15	1	9
15.5—20	1	11
20.5—25	2	28
25.5—30	5	33
30.5—35	5	25
35.5—40	8	30
40.5—45	13	26
45.5—50	2	12
50.5—55	—	3
55.5—60	1	1

ent. In order to find out whether a so-called relative lymphocytosis occurred I have assembled the lymphocyte values obtained in table 4. In the cases in which several differential counts were made the highest value has been taken.

As regards these lymphocyte values it can be said that no counts over 60 per cent were made; in other words, there were no values over the upper borderline stated by Osgood to be a normal lymphocyte percentage. In 9 cases, on the other hand, low lymphocyte values were observed. The number of differential counts made, however, were too few to allow definite conclusions to be drawn.

Eosinophilia was present in 3 of the 38 cases of chronic poisoning. In one of these cases with eosinophilia the patient had bronchial asthma. In the other men working with benzene an eosinophilic picture was encountered 11 times in 141 cases. Eosinophilia was considered to be present when values higher than 6 per cent were obtained. An unusual number of eosinophils in the blood is obviously not a particularly common manifestation in persons suffering from benzene effects.

A study of the hematologic data in the case reports relative to chronic poisoning reveals considerable variations, especially in the number of white blood cells. In all probability these divergences correspond only to a small extent with variations in the degree of intoxication. They can be explained in part by the want of accuracy in the hematologic methods. In healthy persons the white

cell count shows considerable variation on different occasions. In persons with benzene poisoning a similar variation, although on a lower level, is also to be expected. Before any statement can be made as to the severity of the leukopenia it is therefore necessary to keep the patient under observation by making repeated tests.

Sternal puncture was done in 6 of the cases of chronic poisoning. (See the case reports.) In all these cases the specimen was rich in cells and no aplastic anemia had thus had time to develop. A common feature for them all was that the erythropoiesis had been very active and that the leukopoiesis was without any striking changes. In 10 cases red cells showing punctate basophilia were observed in the peripheral blood.

As regards the treatment of these patients with chronic poisoning, this has consisted in 27 instances in removing them for some length of time from operations involving the use of benzene. Patient no. 2, a man under age, went over to another occupation. Of the 26 others, 7 have returned to work but are still having their blood values taken regularly, and 19 have not yet been allowed to start exposing themselves to benzene vapors again; in one of these cases the man has been away from the work for eleven months. In addition to this, the men have been given iron and liver preparations, both by injection and by the oral route. The liver treatment has not caused any noticeable improvement in the blood values but the patients report themselves that they feel better for it. Ten patients with chronic poisoning were admitted to the Clinic and 6 of these were given blood transfusions.

One patient died (case 29). Four months after being examined at the Medical Out-Patient Service at Karolinska Sjukhuset, at which time the blood values were normal, he became feverish and ill in connection with gingivitis and died about a fortnight later of agranulocytosis.

The commonest subjective symptoms from which the patients suffered are assembled in table 5. The figures indicate the frequency of the different symptoms. The patients are classed into three groups in the table, viz. the cases of chronic poisoning, the patients whose anamnesis contained mention of acute poisoning but who do not belong to the chronic poisoning group, and finally other patients (observation cases).

Table 5.

Group of cases	No subjective symptoms	Fatigue	Headache	Vertigo	Nervousness	Insomnia	Gastrointestinal disturbances	Signs of acute poisoning in anamnesis	No. of patients
Chronic poisoning	10	22	2	3	3	1	3	11	38
Acute poisoning in anamnesis	23	31	10	6	3	3	3	61	61
Others	42	31	9[1]	5	3	5	4	—	81

[1] One patient had edema of the papillae and was sent to the neurologic department for examination.

According to this table, in about one-fourth of the cases of chronic poisoning the patients complained of no illness. The predominant subjective symptom was fatigue. The patients felt that after an ordinary day's work they were abnormally exhausted and had no strength left for any outside interests. This feeling of fatigue was often encountered (in about one-half to one-third of the cases), and occurred in all three of the above-mentioned groups. Thus it is obviously not possible, from the subjective symptoms, to weed out those who are suffering from chronic poisoning from among a personnel exposed to benzene. It is quite a different matter, of course, with acute intoxication, in which, in the mild forms in question here, the subjective symptoms constitute the main guide to diagnosis.

Case reports.

1) A, A. G. b. 1902.

   Engraver.

   Duration of employment: 8 years.
   Symptoms of acute poisoning: 0.
   Subjective symptoms: Fatigue.
   Complications: Eczema.

   Sternal puncture Mar. 18. Specimen rich in cells. Erythropoiesis
   active and normoblastic. Leukopoiesis normal.

   Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 18/3	4	50.5 `	3.5		6	36

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
18/3	12.7	4.2	6,000	75,000 90,000	
13/10	14.2	4.5	4,000	160,000	
9/11	14.2	4.4	4,500	200,000	
1/12	12.7	3.9	5,200	190,000	
8	13.1	4.1	5,000		
15	13.1	3.9	10,000		
21	13.0	3.8	4,200	245,000	
28	13.8	4	4,700		
1944 4/1			5,500		
11	13.8	3.9	4,800	190,000	
25	13.8	4.1	5,000		

   Diagnosis: Mild anemia + thrombopenia.

2) A, K. E. b. 1928.

   Rubber worker.

   Duration of employment: 2 weeks.
   Symptoms of acute poisoning: 0.
   Subjective symptoms: 0.

Differential count:

Date		Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	
1943	31/8		43.5	12		4	40.5	
	13/9		60.5	4.5		8.5	26.5	Reds normal
	4/10	1.5	50	4		6	38.5	Reds normal

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
31/8	12.5	4.7	3,800	185,000	
2/9			3,800		
4			3,600		4/9 —
7			4,600		
13			4,800		
20			4,000		
27			5,000		
4/10			4,600	210,000	
26		·	7,600	··	
22/11			4,400		Under age. Benzene exposure terminated.

Diagnosis: Mild leukopenia.

3) A, K. L. b. 1912.

Engraver.

Duration of employment: 4 years.
Symptoms of acute poisoning: Yes.
Subjective symptoms: Tired and nervous.

Differential count:

Date		Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1942	16/2	2.5	75	0.5		2	20
1943	25/6	1.5	55.5	4.5		4	34.5
	30/10		59.5	4.5		3	33

1 stippled red/100 whites, otherwise normality.

Date		Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
1942	16/2	13.1	5	5,000		
1943	25/6	12.7	4.6	4,200	185,000	

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
24/7	12.7	4.4	4,400		
1/10	12.7		3,500		.
13			3,000	200,000	
20			3,200		
30			3,400		1/11 —
8/11			3,000		
29			3,000		
3/12	12.1		4,000	170,000	
13	13.1	4.7	3,600		
1944 4/1	12.4	4.4	3,500	150,000	
19	13.0	4.4	3,800	160,000	Still away from work

Diagnosis: Mild anemia + leukopenia.

4) B, J. H. b. 1910.

Web press assistant.

Duration of employment: 7 years.
Symptoms of acute poisoning: ?
Subjective symptoms: Fatigue.
Complications: Eczema since 1937 — according to dermatologists occupational eczema.
Sternal puncture Mar. 13. Moderate amount of cells in specimen. Erythropoiesis very active; abundant normoblasts. No megaloblasts. Leukopoiesis: Nothing remarkable.

Differential counts:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	Metamyelocytes
1943 13/3	3.5	81			5	10.5	
22	5	72.5	4.5	0.5	5	12.5	
16/4	10	64.5	1.5	0.5	2	21.5	
29	8	63	1.5		4	23	0.5
5/6	25	29	6		13	27	

1943 13/3: Marked aniso-, (macro-,) and poikilocytosis. Slight polychromasia. No stippled or nucleated red cells.

22: Red blood the same as before.

16/4: Marked aniso- and poikilocytosis. Slight polychromasia.

29: 1 polychromatic normocyte to 200 cells.

5/6: Definite anisocytosis. 1 nucleated red to 200 whites.

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	Metamyelocytes
10/8	19	33	5		15	28	

Anisocytosis. A few poikilocytes. No nucleated reds.

7/9 No stippled reds. No polychromasia.

2/11 Definite anisocytosis, no megalocytes, a little polychromasia, no stippled or nucleated red cells.

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
13/3	8.3	2.6	4,100	70,000	13/5 —
				75,000	
22	8.3	3.0	3,800	90,000	
16/4	7.6	2.5	2,400		
22	7.2	2.2	2,000	45,000	
27	6.9	2.1	2,000		
29	7.6	2.2	2,300	48,000	
1/5	9.0	3.5			
2	8.3	2.6	1,400		
4	9.0	2.6	1,400		
6	11.0	3.5	2,200		
7	11.0	3.5	1,800		
8			1,800		
11	11.7	3.7	1,600		
13			1,800		
14	13.1	4.0	2,100		
17	13.8	4.5	2,400	25,000	
19	13.8		2,500		
21	13.8	3.8	2,900		
22			3,000		
24	13.1	3.8	3,400		
25			3,400		
26	12.4	4.0	3,100		
27			2,700		
28	11.7	4.1	3,200		
31	11.7	3.8	3,800		
5/6	9.7	3.8	2,500	30,000	
21	10.0	3.3	3,000		
6/7	9.0	3.3	2,800	60,000	
15	9.2	3.4	2,100		
6/8	9.0	3.0	4,200	58,000	
10	9.0	2.5	2,200	27,000	
12	9.6	3.5	3,400	25,000	
17			3,400		
19	9.4	2.5	2,400	78,000	

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
23			4,200		
24			3,300		
26	9.6	2.6	2,300	48,000	
28			2,400		
31	11.8	2.7	2,900	48,000	
4/9			3,500	30,000	
7	11.8	3.0		30,000	
9			2,000		
11			3,900		
14	12.8	3.2	2,600	46,000	
16			3,500		
18			3,500		
22	13.5	3.2	3,700	55,000	
28	15.8	4.1	5,000	48,000	
30			3,000		
2/10			3,400		
4	13.4	4.3	5,500	57,000	
14			5,400		
20	11.3	3.8	5,000	70,000 ·	
2/11	12.2	3.9	5,000	80,000	
16	12.4		4,800	85,000	
4/12	12.7		4,500	80,000	
20 ·	13.0	4.2	3,800	80,000	
30	13.8	4.2	2,800	70,000	
1944 3/1			4,200		
10	14.5	4.3	4,000	110,000	
1/2	10.4?	3.2	5,600	107,000	
2	12.5	4.2	5,200		Still away from work

Diagnosis: Anemia + leukopenia + thrombopenia.

5) B, B. G. b. 1906.

Rubber worker.

Duration of employment: 1924—1932 and then since Aug. 1942.
Symptoms of acute poisoning: 0.
Subjective symptoms: 0.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 1/9	2.5	51	2.5		5	39
4/10		59.5	0.5		4	36

3 stippled reds/100 whites. Slight anisocytosis.

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
1/9	14.5	4.8	3,400	115,000	
3			3,600	110,000	
9			4,000	110,000	9/9 —
16			4,200		
28			4,200		
4/10			3,400	140,000	— 9/10
30			4,200		
27/11			6,400		
30/12	15.3	4.8	3,600	130,000	
1944 8/1			4,600		
11			4,800		
22			3,000		

Diagnosis: Mild leukopenia.

6) B, E. A. b. 1896.

Intaglio printer.

Duration of employment: 30 years.
Symptoms of acute poisoning: 0.
Subjective symptoms: Fatigue.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 29/3	1.5	40	5.5		6	47

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
29/3	14.1	4.6	2,800	220,000	
				210,000	
31			2,400		
7/5			3,400		
2/6			4,500		
19			3,700		
2/8	13.1	4.4	4,100	225,000	
17			4,000		
6/9			4,800		
20	13.8	4.8	4,800	220,0000	
13/10			5,900		
3/11	13.1	4.6	3,800	210,000	

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
17			3,600		
24			4,500		
1/12	13.1	4.4	4,600	190,000	
14			3,400		
28	13.8	4.6	4,100	200,000	
1944 18/1			4,300		

Diagnosis: Leukopenia.

7) B, T. b. 1902.

Assistant pressman.

Duration of employment: 7 years and 4 months.
Symptoms of acute poisoning: Nothing definite.
Subjective symptoms: Fatigue.
Complications: Neurasthenia.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	
1943 31/3		59.5	4.5		6.5	29.5	Reds normal
5/10		46.5	6.5		5	42	

Red blood: Slight macrocytosis.

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
31/3	14.1	4.9	3,000	225,000	
2/4			2,900		
5/5			3,200		
29			3,500		
6/7			2,500		6/7 —
20	13.8		3,400	245,000	
18/8	13.4	4.4	2,600	200,000	
19			4,800		
21			3,400		
26			2,800		
28			3,600		
3/9			3,600		
9			3,200		
16	13.5	4.4	3,000	195,000	
24			3,200		
5/10			2,200	180,000	

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
7	11.7	5.0	5,000		
11	12.8	5.2	5,200		
20			5,000		
28			3,600		
15/11			3,400		
4/12			4,400		
20	14.1	4.5	2,800	190,000	
22			4,000		
1944 4/1			3,600		
12	13.8	4.4	2,600	180,000	
28	13.8		4,000		Still away from work

Diagnosis: Leukopenia + neurasthenia.

8) B, H. N. G. b. 1905.

Pressman.

Duration of employment: 1 ½ years.
Symptoms of acute poisoning: 0.
Subjective symptoms: 0.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 8/3	1.5	66.5	3.5		6.5	22

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
8/3	12.8	4.5	6,500	190,000	
11				170,000	
22/11	11.7	4.7	4,200	150,000	
29	11.0	4.4	5,800		
6/12	12.1	4.5	3,600		
13	12.4	4.4	3,200	155,000	
15			3,600		15/12 —
1944 3/1	12.2	4.5	3,300	145,000	
7	12.2	4.7	5,300		
14	13.0	4.5	3,000		
31	13.0	4.5	4,900	175,000	Still away from work

Diagnosis: Anemia + leukopenia.

9) B, P. O. A. b. 1912.

Rubber repairer.

Duration of employment: 2 years.
Symptoms of acute poisoning: Yes.
Subjective symptoms: Fatigue.

Differential count:

Date		Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	
1943	6/9	2.5	65	1		5	26.5	Reds normal
	4/12	2	62	4.5		4.5	27	Reds normal

Date		Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
	6/9	14.1	5.2	3,800	120,000	
	10			4,000		
	18			3,400		
	9/10			5,300	165,000	
	6/11			4,400		
	27			3,000		
	4/12	13.1		3,000	135,000	
	16	13.5	4.7	3,600	135,000	
1944	8/1			2,500		
	10			4,900		
	24	14.5	5.1	3,800	155,000	

Diagnosis: Leukopenia.

10) C, O. F. b. 1898.

Intaglio printer.

Duration of employment: 27 years.
Symptoms of acute poisoning: 0.
Subjective symptoms: Fatigue.

Differential count:

Date		Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	Macrolymph. of various kinds
1943	22/3	1.5	52	2.5	0.5	7.5	30.5	5.5
	22/9		64	0.5	0.5	9.5	25.5	
								Reds normal
	16/11		51	0.5		7	41.5	
								Slight macrocytosis

Date	Hb g/100 cm³ blood	Reds mill./mm³	Whites pr mm³	Thrombocytes per mm³	Away from work
22/3	13.7	4.4	3,200	180,000 190,000	
24/5			3,600		
27/7	13.7	4.4	2,200	170,000	
29			2,400		29/7 —
3/8	12.4	4.3	4,300	150,000	
6			2,700		
11			4,300		
18			3,800		
25			3,600		
1/9			4,000		
15	13.7	4.3	2,600		
22			4,200		
28			3,400		
15/10			3,200	220,000	
26			3,200		
2/11			3,600		
16			3,400		
30			4,800		
13/12	12.2	4.1	4,000	175,000	
21	13.0	4.2	3,800		
1944 4/1			3,800		— 5/1
11	13.8	4.5	4,400	155,000	
18			4,200		
26	13.0	4.1	3,600		

Diagnosis: Moderate anemia + leukopenia.

11) C, N. B. b. 1889.

Assistant pressman.

Duration of employment: 2 years. Had a break during past year but had been at work again 1 month.
Symptoms of acute poisoning: Yes?
Subjective symptoms: 0.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 6/8	5	62.5	1.5		8	23

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
6/8	14.1	4.7	6,200	200,000	
21			3,400		
27			4,100		
4/9			3,600		
9	13.8	4.5	5,600	195,000	
16			4,100		
29			4,400		
18/10	13.5	4.6	4,500	235,000	
10/11			4,200		
1/12	13.4	4.7	6,500	250,000	
8			5,900		
22	13.8	4.4	3,500	225,000	
28			3,800		
1944 12/1	13.0	4.4	3,400	200,000	

Diagnosis: Leukopenia.

12)   E, E. J. b. 1917.
      Lithographer.

      Duration of employment: 6 years.
      Symptoms of acute poisoning: 0.
      Subjective symptoms: 0.

      Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	
1943 3/8	2	48.5	3.5		3	43	Reds normal
3/12		39	2.5		2.5	56	Reds normal

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
3/8	13.5	4.7	2,600	150,000	
5			3,200		5/8 —
16			6,400		
23			6,800		
6/9	14.1	4.8	3,600	185,000	
17	14.5	4.8	3,600	210,000	
27			6,000		
8/10			4,300	195,000	
19			5,100	180,000	
1/11			3,800		
18			4,700		
3/12	13.4		4,400	220,000	
18	14.1	4.7	4,600		— 19/12

1944 18/1	15.3	4.8	5,700	245,000
25			4,500	

Diagnosis: Leukopenia.

13) E. K. E. b. 1908.

Laboratory assistant.

Duration of employment: 1 year.
Symptoms of acute poisoning: ?
Subjective symptoms: Vertigo.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 7/6	1	74			5.5	19.5

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
7/6	14.5	5.1	3,600	232,000	
9			3,800		
22			5,100		

Diagnosis: Leukopenia.

14) E. T. E. b. 1901.

Engraver.

Duration of employment: 26 years.
Symptoms of acute poisoning: 0.
Subjective symptoms: Fatigued for a whole year. Impotent. Easily
acquired bruises. On Aug. 9 purpura haemorrhagica (petechiae
on lower legs).
Sternal puncture Aug. 23. Specimen rich in cells. Erythropoiesis very
active. Among the basophil normoblasts there were a few with a
loose nucleus resembling megaloblasts. Leukopoiesis normal.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 21/5	7	48.5	3.5		2	41

Aniso-, macro-, and poikilocytosis, no polychromasia, no
stippled or nucleated reds.

10/8	7	45	3		3	42

Anisocytosis, a few poikilocytes, no nucleated reds.

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
21/5	13.1	4.2	4,200	95,000	
				150,000	
15/6	14.3	4.5	3,300	65,000	
22			4,200	70,000	
				50,000	
27/7	13.1	3.9	3,600	35,000	
29			3,000	50,000	
2/8	12.7	4.0	5,500	80,000	
9			3,900	30,000	
10	11.7	3.5	3,200	36,000	10/8 —
12	12.4	3.6	6,200	39,000	
14				35,000	
17			5,000		
19	11.5	3.3	3,700	70,000	
23			3,800		
24			6,400		
26	11.5	3.5	3,500	35,000	
30	12.1	3.6	4,100	46,000	
6/9			3,500	60,000	
23	13.1	4.0	3,400	60,000	
15/10			2,200	75,000	
22			3,500	50,000	
1/11			3,200	85,000	
15			5,400	75,000	
8/12	11.7		4,900	85,000	
1944 11/1	13.0	3.9	3,800	110,000	
28	12.2	3.7	3,400	85,000	Still away from work
1/2			6,500		

Diagnosis: Anemia + leukopenia + thrombopenia.

15) F, O. G. L. b. 1914.

Intaglio printer.

Duration of employment: 8 years.
Symptoms of acute poisoning: Yes.
Subjective symptoms: Fatigue.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	
1943 26/5	2	57.5	5.5		7	28	Reds normal

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
26/5	12.7	4.5	3,800	205,000	
29			4,800		
4/6			3,700		
13/8	12.4	4.5	3,800	210,000	13/8 —
19			3,200		
25			4,000		
8/9	13.1	4.4	3,600	150,000	
22			6,200		— 23/9
15/10			4,200		
15/11	13.1	4.7	5,200	140,000	
29	13.1	4.6	5,700	135,000	
6/12			4,400		
13			5,600		
20	10.3	4.1	4,400	160,000	
28	12.3	4.1	3,500		
1944 3/1			8,000		
10	13.0	4.4	8,700		
17			4,000		
31	13.0	4.3	4,400	190,000	

Diagnosis: Anemia + leukopenia.

16) H, B. W. b. 1904.

Engraver.

Duration of employment: 21 years.
Symptoms of acute poisoning: 0?
Subjective symptoms: Moderate anginoid pains.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	Myel.
1943 16/8		63.5	1.5		9.5	25	0.5
						Reds normal	
20/10	1.5	51.5	3		6	38	

Slight macrocytosis. 2 stippled reds/100 whites.

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
16/8	12.7	4.6	5,000	240,000	
30/9			3,400		
20/10	12.7	4.4	4,200	190,000	
9/11			4,400		
13/12	13.1		3,800	225,000	

Diagnosis: Moderate anemia + leukopenia.

17) H, O. V. b. 1915.

Assistant to intaglio printer.

Duration of employment: 7 years.
Symptoms of acute poisoning: 0.
Subjective symptoms: 0.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	
1943 21/4	1	53.5	4.5	0.5	4.5	36	Reds normal

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
21/4	13.1	4.8	3,000	150,000 155,000	
30/7	13.8	4.8	4,500	120,000	
6/8			3,400		
9			3,600		9/8 —
16			3,700		
7/9			4,000		
21	14.1	4.8	3,200	145,000	
4/10			5,200		Military
11			6,400		service
25			5,000		about 1/10
1/11			5,800		
4/12			5,600		
1914 8/1			2,300		
10	15.3	5.0	5,200	170,000	

Diagnosis: Leukopenia.

18) J, F. K. H. b. 1911.

Assistant to intaglio printer.

Duration of employment: 14 years.
Symptoms of acute poisoning: 0.
Subjective symptoms: 0.
Complications: Eczema.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 20/3		63.5	2		8.5	40.5
1/12		68	6		1.5	24.5

Slight anisocytosis. No stippled reds.

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
20/3	12.7	4.7	5,000	200,000 180,000	
24/9	12.8	4.6	6,700	180,000	
22/10			2,600		
15/11	11.6	4.3	4,600	160,000	
22	11.3	4.3	3,800		
27			5,000		
29	10.8	3.9	4,000		
1/12	11.0	3.9	3,000	150,000	1/12 —
15	11.7	3.9	4,200	170,000	
28	13.0	4.1	5,300	180,000	
1944 17/1	12.2	4.0	3,200	180,000	
25			4,800		Still away from work

Diagnosis: Anemia + leukopenia.

19) J, N. M. b. 1886.

Intaglio printer.

Duration of employment: 19 years.
Symptoms of acute poisoning: Yes.
Subjective symptoms: Increased flow of saliva, nausea, fatigue.
Complications: Duodenal ulcer?

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	
1943 4/5	6	43.5			14	36.5	Slight aniso-cytosis
8/11	3	61	3		8	25	Slight aniso-cytosis

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
4/5	11.3	3.9	3,000	155,000 165,000	
8			6,500		
18			8,000		
5/6	12.2	4.1	4,800		
22	11.5	3.8	3,500	88,000	
17/7	12.2	3.9	6,000		
20				100,000	
21/8	12.7	4.1	4,000	120,000	

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
25			4,500		
4/9			3,800		4/9 —
11			5,600		
18	12.2	4.1	3,500	170,000	
29			4,700	120,000	
14/10	13.1	4.4	5,300		— 19/10
28			3,600	125,000	
8/11			5,000		
8/12			5,200		
1944 18/1	13.0	4.3	6,000	165,000	

Diagnosis: Anemia + leukopenia + thrombopenia.

20) J, S. E. A. b. 1913.

Assistant to intaglio printer.

Duration of employment: 4 years.
Symptoms of acute poisoning: 0.
Subjective symptoms: Pains in back, otherwise none.
Complications: Insufficientia dorsi.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 6/4	7.5	40.5	4.5		4	43.5

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
6/4	13.5	4.8	3,200	200,000	
1944 17/1	14.5	4.9	4,000	160,000	
24			4,200		
31	13.0		4,700		
2/2	13.0	4.4	3,000	160,000	
9	11.5	4.3	2,300	180,000	10/2 —

Diagnosis: Anemia + leukopenia.

21) K, O. B. b. 1916.

Web press assistant.

Duration of employment: 8—9 years.
Symptoms of acute poisoning: 0.
Subjective symptoms: 0.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 20/3	3	43.5	4.5		8.5	40.5

Date	Hb. g/100 cm³ blood	Reds mill/mm³	Whites per mm³	Thrombocytes per mm³	Away from work
20/3	14.1	4.9	7,600	165,000 170,000	
2/8	14.1	4.6	2,600	160,000	
4			4,600		
7			3,400		7/8 —
16			4,800		
30			3,000		
4/9			4,700		
10	14.4	4.7	6,000	175,000	
21			5,800		
12/10	13.4	4.7	5,700	200,000	
18			7,400		
25			6,500		
9/11	13.4	4.6	5,500	220,000	Military service 10/11-20/12
21/12	14.5	4.8	7,000	205,000	— 21/12
1944 4/1			4,000		
19	14.5	4.7	6,200	245,000	

Diagnosis: Leukopenia.

22) L, A. E. b. 1883.

Mechanic.

Duration of employment: 2 years.
Symptoms of acute poisoning: 0.
Subjective symptoms: 0.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	
1943 25/8	3	55.5	1		5	35.5	Reds normal

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
25/8	11.5	4.1	3,800	200,000	
4/9	11.3	4.1	4,600		
11			7,200		
1944 3/1	10.7	3.8	9,600	215,000	
8	11.0	4.0	4,800		
18	10.7	3.8	5,400	230,000	

Diagnosis: Anemia.

23) L, J. T. V. b. 1891.

Pressman.

Duration of employment: 6—8 mths. 1941, and now since Aug. 1, 1942.

Symptoms of acute poisoning: Yes.

Subjective symptoms: Headache, dizziness, fatigue.

Complications: Neurasthenia.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	
1943 13/4	6.5	49.5	0.5		7.5	35.5	Slight aniso-cytosis
8/7	Red blood picture showed fairly definite macrocytosis.						
1944 24/1	8	60			7	25	

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
1943 13/4	12.4	3.8	3,800	120,000 140,000	
22/5	12.1	3.6	2,400		
28			4,800		
5/6	12.2	3.6	3,900		5/6 —
18	12.8	3.7	5,500		
2/7	13.1	3.8	3,400		— 19/7
4/11	11.7	3.9	3,800	90,000	
15			4,400	170,000	
6/12	13.0	4.3	3,400	140,000	
13	13.0	4.4	6,500		
20	13.0	4.4	3,400	130,000	
28	13.0	4.2	3,800	140,000	
1944 3/1			3,800		
10	12.3	4.0	4,300		
17	12.3	3.8	7,500	150,000	
19	11.5	3.7	4,000		19/1 —
25	12.3	4.7	5,000		
1/2				81,000	Still away from work

Diagnosis: Anemia + leukopenia + thrombopenia + neurasthenia.

24) L, K. H. O. b. 1900.

Lithographer.

Duration of employment: 2 ½ years.

Symptoms of acute poisoning: 0.

Subjective symptoms: 0.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 27/5	2	54.5	2.5		4.5	36.5

Slight unevenness in size of red cells, a few polychromatic reds. About 15 stippled reds/200 whites.

| 4/6 | No stippled reds. |

2/7 Very slight unevenness in size of red cells. No polychromatic reds. No stippled reds.

| 26 | 6 | 44.5 | 4.5 | | 4 | 41 |

Red blood picture: Slight macrocytosis.

| 13/10 | 2.5 | 43.5 | 13 | | 6 | 35 |

7 stippled reds/100 whites. Slight poikilo- and anisocytosis.

| 28/12 | | 56 | 1.5 | | 2.5 | 40 |

Slight anisocytosis.

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
27/5	13.3	4.4	3,000	210,000	
29			2,800		
4/6			4,500		
2/7			3,800		
12			2,800		
26	12.4		3,800	200,000	
31	12.2	4.0	2,800		31/7
2/8	12.7	4.0	2,800		
4			3,800		
24	13.1	4.1	4,000	180,000	
31			5,000		
14/9			3,800		
29			4,000		
13/10			3,500	150,000	
28			5,000		
8/11			3,600		
15			3,600		
6/12	13.1		4,000	140,000	
28	13.8	4.0	4,300	200,000	— 5/1
1944 24/1	12.3	3.7	4,000	210,000	
31	12.3	3.6	3,800		
3/2	12.6	3.8	1,600	152,000	3/2 —

Diagnosis: Anemia + leukopenia.

25) L, S. W. b. 1913.

Engraver.

Duration of employment: 13 years.
Symptoms of acute poisoning: Yes?
Subjective symptoms: 0.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 5/4	3.5	79.5			3.5	13.5

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
5/4	12.4	4.3	8,200	140,000 145,000	
8/10			5,500		
5/11			4,200		
22	12.4	4.2	3,500	155,000	
29	12.0	4.0	5,000		
6/12	11.7	4.2	4,600		•
13	11.7	4.0	5,000	155,000	
20	11.5	4.2	6,600		
28	12.3	4.4	4,500		
1944 10/1	13.0	4.4	5,300	165,000	•
24			5,400		

Diagnosis: Anemia.

26) L, P. E. b. 1897.

Intaglio printer.

Duration of employment: 30 years.
Symptoms of acute poisoning: Nothing definite.
Subjective symptoms: Fatigue, vague gastro-intestinal discomfort.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	
1943 8/4	5.5	55.5	5.5		6	27.5	Reds normal
14/10	1.5	57.5	3.5		5.5	32	

5 stippled reds/100 whites. Red cells otherwise normal.

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
8/4	13.2	4.6	2,800	175,000 185,000	

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
22/5			2,200		
29			4,000		
4/6			3,500		
22			4,100		
23	13.1	4.4	2,800		
10/8			4,600		
25			7,900		
17/9	13.2	4.4	4,400	175,000	
1/10			3,200	135,000	1/10 —
14			3,200	165,000	
28			4,500		
12/11			4,400		
10/12			4,600		
1944 4/1	13.0	4.2	3,600	155,000	
10	13.8	4.4	3,600	190,000	
22			5,600		Still away from work

Diagnosis: Leukopenia.

27) L, G. E. H. b. 1907.

Foreman.

Duration of employment: 17 years.
Symptoms of acute poisoning: ?

Subjective symptoms: Fatigue, headache, vertigo, waves of nausea.
Complication: Concussion of the brain in 1942.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	
1943 20/10	1	63	2.5	0.5	3	30	Very slight anisocytosis
4/11		75.5	2		4	18.5	A few macrocytes

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
20/10	12.4	4.5	3,400	205,000	
26			3,200		
4/11			3,700		
16			4,200		

Diagnosis: Leukopenia (Concussion of the brain in 1942).

28)   M, C. R. V. b. 1906.

Intaglio printer.

Duration of employment: 20 years.
Symptoms of acute poisoning: 0.
Subjective symptoms: Fatigue.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 31/5	2	56	2.5	0.5	4	35

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
31/5	12.8	4.7	3,300	229,000	
11/6			5,800		
3/7			5,800		
20			3,400		
3/8	13.4	4.6	3,900	180,000	
17			3,000		17/8 —
20			5,800		
3/9			5,600		
17	13.4	4.5	3,400	190,000	
28			3,800	200,000	
5/10			3,200		
16			4,700		
28			3,000		
17/11			3,200		— 18/11
13/12	13.1	4.3	4,500	260,000	
20			4,200		
28	13.0	4.3	5,000		
1944 3/1			4,800		
17	13.0	4.5	4,200	205,000	
24			4,400		
31			5,500		

Diagnosis: Leukopenia.

29)   M, H. L. A. b. 1897.

Intaglio printer.

Duration of employment: 20 years.
Symptoms of acute poisoning: 0.
Subjective symptoms: Fatigue.

Differential count:

Date		Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943	19/3	4	62.5			8	25.5

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
19/3	13.0	4.4	5,300	165,000 165,000	

After being examined at Karolinska Sjukhuset the patient continued with his work. Four months later he fell ill, with tenderness and a pain in his mouth and a temperature of about 39° C. About 4—5 days later he was admitted to another hospital (The Sabbatsberg Hospital; head physician Dr. Nylin) suffering from gingivitis and with a temperature of 39.9° C. but with no abnormal signs in the tonsils. For the blood values, see below. He was treated intensively with blood transfusions, liver and vitamin preparations, and bone marrow preparations, but he died after being in the hospital for 10 days, showing all the signs of agranulocytosis.

Differential count:

Date		Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	Immature unclassified cells	Metamyelocytes
1943	24/7		28			2	70		
	27		38	1		1	58	2	
	28		43	1			55	2	
	31		14	4		6	74		2

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
23/7	7.7	2.5	1,200		
24	7.7	2.2	1,000		
25			650		
26	8.3	2.8	430	181,000	
27	10	3.1	530	225,000	
28	10.4	3.2	680		
29	10	3.1	500	201,000	
30	10	3.1	860	376,000	
31	8.8	3.1	770	424,000	
1/8	8.0	2.9	580		

Diagnosis: Granulocytopenia + anemia.

It can hardly be doubted that there was a causal connection between the benzene exposure and disturbances in the blood in this patient. Idiopathic granulocytopenia does not go hand-in-hand with anemia.

It is not known how long this condition had taken to develop. In all probability, however, it had existed for less than 4 months.

30) P, C. b. 1899.

Intaglio printer.

Duration of employment: 19 years.
Symptoms of acute poisoning: ?
Subjective symptoms: Fatigue, poor sleep, rhinitis sicca, periodical stomach pains.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 7/4	6.5	54	2		5	32.5

Slight anisocytosis and polychromasia. 1 stippled red blood cell per 100 whites.

7/10	7	53	1		1	38
2/11	2.5	40	5		8	44.5

Slight anisocytosis. 3 stippled reds/100 whites.

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
7/4	10.8	3.7	3,000	85,000 95,000	
16	10.8	3.6	2,800	90,000	27/4 —
13/5	11.5	3.7	2,600		
27	11.7	3.9	2,200		
15/6	12.8	4.2	2,600		
21	12.3	4.1	2,000		
26			3,000		
5/7	11.3	3.8	3,000	140,000	
26	12.4	4.0	3,400	115,000	
10/8	12.0	3.9	3,800	140,000	
21	12.0	4.0	5,000		
28			3,600		
4/9	12.1	4.0	5,000		

Date		Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
	18		•	3,800		
	29			2,800	· 105,000	
	5/10	9.7	4.1	2,000		
	7			3,600		
	11			3,200		
	13	13.1	4.4	3,800		
	15			3,800		
	20			4,400		
	2/11			2,400	120,000	
	11			3,400		
	3/12			6,000		
	15		·	3,800		
1944	5/1	13.0	4.1	3,200	115,000	
	20	13.0	4.4	3,900	90,000	Still away
	3/2	11.2	4.0	4,400	113,000	from work

Diagnosis: Anemia + leukopenia + thrombopenia.

31)   P, R. b. 1911.

Engraver.

Duration of employment: 12 years.
Symptoms of acute poisoning: Yes.
Subjective symptoms: Nervous, easily roused to anger.
Sternal puncture Apr. 21. Specimen rich in cells. Erythropoiesis
active; abundant normoblasts. In places, the specimen contained
cells displaying highly basophil. protoplasm and a fairly loose
nucleus but no definite nucleoli. Reticulum cells? Leukopoiesis
normal. Reticulum hyperplastic? An increase in the number of
megakaryocytes. Sternal puncture Aug. 23. Specimen rich in
cells. Erythropoiesis active. Among the basophil normoblasts
there were a number with a fairly loose nucleus. Leukopoiesis
normal.

Differential count:

Date		Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	
1943	20/4		70.5	·3.5		4.5	21.5	Slight aniso- cytosis
	2/7	2	59.5	3.5		3	32	
	12/10	1.5	65			6 ·	27.5	Slight aniso- cytosis

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
1943 20/4	12.1	4	2,400	265,000	
21			2,200		
7/5	12.1	4.3	1,600		7/5 —
15			2,600		
22	12.7	4.4	2,000		— 22/6
26			3,000		
2/6	13.3	4.3	4,500	122,000	
				136,000	
21	14.0	4.7	5,000		
2/7			3,100	205,000	
29	13.1	4.7	1,800	165,000	29/7 —
30			2,800		
2/8	11.7	4.3	2,400	170,000	
6			2,500		
12			2,200		
16	13.1	4.1	3,400	156,000	
17				100,000	
23			3,200		
24	12.7	4.6	3,500	76,000	
26			3,400		
28			2,800		
30	12.4	4.2	2,800	72,000	
6/9			3,000		
25			4,000		
12/10			3,000	165,000	
3/11			4,400		
2/12			4,000		
14	14.5	4.3	3,800	120,000	
29	13.8	4.3	4,200	165,000	
1944 18/1	13.0	4.4	3,500	180,000	Still away from work

Diagnosis: Anemia + leukopenia + thrombopenia.

32) P, K. F. b. 1903.

Lithographer.

Duration of employment: 3 years.
Symptoms of acute poisoning: Yes.
Subjective symptoms: Fatigue.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	Macrolymph. of various kinds	Myel.
1943 30/3	4.5	72	1.5		4.5	13.5	4	
17/6	2	59	1		5	33		
28/9		66.5			7.5	25.5		0.5

Slight polychromasia and macrocytosis. 2 stippled reds/100 whites.

| 9/11 | | 53 | 0.5 | 0.5 | 6 | 40 | | |

Slight macrocytosis.

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
30/3	12.0	4.0	5,400	105,000	
				90,000	
1/4			3,400		
22/5	10.2	3.3	4,000		22/5 —
29	10.2	3.6	3,400		
31	9.7	3.2	4,700		
8/6	9.0	3.0	2,000		
10	11.7	4.2	4,500	70,000	
17	13.1	4.6	4,500	62,000	
21	12.4	4.6	4,500	62,000	
5/7	12.1	4.1	5,000	95,000	
19	12.4	4.3	5,400	80,000	
31	12.1	4.0	3,600	90,000	— 20/7
7/8	12.1	4.0	3,200	90,000	7/8 —
14			3,500		
23	12.0	4.2	4,800	70,000	
7/9			3,800		
20			3,800		
28	12.1		3,600	90,000	
11/10			4,600		
25			5,200		
9/11			4,200	115,000	
7/12	12.7		3,000	80,000	
20	12.4	4.3	4,000	105,000	
1944 4/1	13.8	4.5	3,900	90,000	
10	13.8	4.4	3,200	135,000	
25			4,300		Still away from work

Diagnosis: Anemia + leukopenia + thrombopenia.

33) ·R, N. H. b. 1904.

Intaglio printer.

Duration of employment: 10 years.
Symptoms of acute poisoning: Yes.
Subjective symptoms: Fatigue.
Sternal puncture Mar. 17. Specimen rich in cells. Erythropoiesis
     very active. No megaloblasts. Leukopoiesis: Nothing abnormal.
Reticulum apparently normal.
Sternal puncture Aug. 23. Specimen rich in cells. Erythropoiesis
     very active. Among the basophile normoblasts there were some
     with a strangely loose nucleus, resembling megaloblasts. Leuko-
     poiesis normal.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	Metamyelo-cytes
1943 17/3	2.5	56.5	1.5		11.5	28	
14/8	9	54	2.5		7.5	26	1
7/10		47.5	1.5		5	46	

Slight polychromasia and macrocytosis. 7 stippled reds/100
     whites.

| 13/12 | 4 | 46 | 2 | | 15 | 33 | |

Slight anisocytosis and polychromasia. 5 stippled reds/100
     whites.

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
1943 17/3	10.8	3.8	4,000	70,000	
				85,000	
23	11.3	3.8	3,400		
29			4,000		
16/4	12.4	4.3	3,000		.
19/5	12.7	4.3	3,600		
19/7	11.7	3.8	2,600		
14/8	.11.3	3.8	1,400	90,000	14/8 —
16	11.7	4.2	3,100		
17	11.7	3.1	3,900	30,000	.
19			4,100		.
22			4,700		
24	12.0	3.4	3,800	34,000	.
26			3,700		
28			5,400		.
30	12.4	4.0	4,000	38,000	.
6/9			3,000		.

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
22			5,300		
7/10			2,400	115,000	
21			2,200		
1/11			2,200	100,000	
19			2,800		
13/12	13.5	3.9	3,000	100,000	
1944 5/1	13.8	4.2	3,800	110,000	
20	13.8	4.2	3,000	95,000	Still away from work

Diagnosis: Anemia + leukopenia + thrombopenia.

34) S, O. L. b. 1917.

Engraver.

Duration of employment: 3 years.
Symptoms of acute poisoning: Yes.
Subjective symptoms: 0.

Sternal puncture May 25. Specimen rich in cells. Erythropoiesis greatly increased, and normoblastic. Leukopoiesis showed no particular changes.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	Macrolymph. of various kinds
1943. 9/4	4	42.5	5.5		7	41	
16/6	4	59	3		5	29	
2/10	6	55.5	2.5		5	30	1

1 stippled red/100 whites

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
1943 9/4	10.8	4.0	3,600	115,000	
				115,000	
21	11.3	4.3	2,800		
15/5			3,200		
19	11.0	3.9	2,000		19/5 —
21	9.7	3.4	1,800		
25	11.0	3.6	1,900	86,000	
27	12.4	3.8	1,800		
31	11.7	3.8	2,500		
8/6	11.0	5.2	3,000		

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
10	12.4	4.8	3,200	76,000	
16	13.1	5.0	3,400	60,000	
21	13.7	4.5	2,200		
9/7	12.7	4.4	2,400	125,000	
20			2,400	185,000	
2/8	12.4	4.1	1,600	160,000	
5	11.7	4.3	1,800		
9	12.7	4.5	2,400	180,000	
12	13.8	4.7	3,200	82,000	
17			3,000		
25			4,800		
3/9			1,600	140,000	
			2,600		
4			3,400		
10			3,000		
24			3,400		
2/10			3,800	115,000	
16			2,700		
2/11			3,800		
16			3,500	150,000	
7/12			4,000		
15	13.0	4.0	3,200	110,000	
1944 11/1	13.0	4.2	3,200	135,000	Still away
31			3,200	145,000	from work
2/2	11.8	3.9	3,400		

Diagnosis: Anemia + leukopenia + thrombopenia.

35) S, A. R. b. 1900.

Intaglio printer.

Duration of employment: 23 years.
Symptoms of acute poisoning: 0.
Subjective symptoms: Fatigue.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	Macrolymph. of various kinds
1943 30/3		55.5	1.5		2	41	Reds normal 5.5
6/12		46	3.5		4	41	Reds normal

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
30/3	13.0	4.6	2,200	235,000	
				245,000	
1/4			4,000		
18/5			4,200		
18/6	13.7	4.9	3,100		
24/7			3,300		
29	13.8	4.4	3,600	190,000	
10/8			4,000		
16			3,000		16/8 —
18			3,400		
23			3,200		
28			2,600		
31			2,700		
4/9	11.7	4.2	3,000		
13			4,800		
27	12.7	4.3	2,800	195,000	
11/10			2,500		
18	13.1	4.3	3,200	150,000	
1/11			2,800		
9			4,500		
29			5,500		
6/12			3,500	145,000	
22	13.0	4.3	2,800	130,000	
28	13.8	4.5	3,400		
1944 17/1	13.0	4.4	6,000		
26	12.3		3,000	195,000	Still away from work

Diagnosis: Anemia + leukopenia.

36) S, A. H. b. 1907.

Engraver.

Duration of employment: 7 years.
Symptoms of acute poisoning: ?
Subjective symptoms: Fatigue, heart palpitation, breathing difficulties.
Complications: Bronchial asthma + allergic rhinitis.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1941 4/2			2.5			
1943 31/5		46	8		13	33

Marked anisocytosis and polychromasia.

22/10	2	52	8.5		6	31.5

Slight macrocytosis and polychromasia.

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
1941 24/3	9.5				
31	10.2				
9/4	12.0		5,600		
2/5	13.5	4.8			
16	13.3	4.4			
1943 31/5	11.9	4.1	3,300	58,000 67,000	
5/6			2,800		
15			2,000		16/6 —
19	11.7	3.2	2,200		
22	13.0	3.6	3,400		
26	12.2	3.6	3,000		
6/7	12.7	3.8	9,200	135,000	
16	11.7	3.6	2,200		
24	12.7	4.5	3,500		
13/8			5,400		
20	13.5	4.8	4,000		
26			3,800		
9/9			4,500		
20	13.5	4.6	4,200	175,000	
7/10			5,500		
22			3,000	110,000	
5/11			4,700		
1/12	12.0	4.2	5,200	150,000	
16			4,100		
1944 7/1	13.8	4.2	3,600	120,000	
19	ʼ13.8	4.4	5,100	175,000	Still away from work

Diagnosis: Anemia + leukopenia + thrombopenia + bronchial asthma + allergic rhinitis.

37)   W, K. H. b. 1910.

Engraver.

Duration of employment: 4 ½ years.
Symptoms of acute poisoning: Yes.
Subjective symptoms: Heart palpitation, constriction in throat, nervous, tired.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.	
1943 5/4		70.5	1.5		10	18	Reds normal
1/11		50	2.5	0.5	5	42	Reds normal

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
5/4	14.4	5.0	6,000	140,000	
				155,000	
31/7	12.4	4.4	3,000	160,000	
11/8			5,000		
25			4,500		
8/9			3,800		
23			6,800		
13/10	11.7	4.2	3,500	165,000	
1/11			3,200	170,000	
10			3,200		
17			5,200		
7/12	12.8	4.2	5,200	190,000	
28	13.0	4.5	4,700	215,000	
1944 26/1	13.0	4.3	4,700	185,000	

Diagnosis: Anemia + leukopenia.

38) V, G. K. F. G. b. 1908.

Engraver.

Duration of employment: 8 years.
Symptoms of acute poisoning: ?
Subjective symptoms: Fatigue, constriction in chest, and breathing
  difficulties.
Complications: Concussion of the brain in 1941.

Differential count:

Date	Staff cells	Segmented cells	Eos.	Bas.	Mon.	Lymph.
1943 24/3	4.5	56.5	3.5		7	28.5
8/12	8	59.5	2.5		5	25

Slight anisocytosis.

Date	Hb. g/100 cm³ blood	Reds mill./mm³	Whites per mm³	Thrombocytes per mm³	Away from work
24/3	12.4	4.5	3,600	170,000	
				150,000	
27			3,600		
21/4	12.7	4.5	3,600		
6/5			3,400		
18			2,600		
10/6			2,500		10/6 —

Date	Hb. g/100 cm³ blood	Reds mill./mm³	White per mm³	Thrombocytes per mm³	Away from work
10/7			3,800		
24	12.7	4.6	3,400		
26/8			3,400		
30	.		2,800		
1/9			5,800	.	
10			5,200		
17	13.3	4.5	3,000	160,000	.
30			3,800	185,000	
15/10			2,600		
21			3,000		
3/11			5,200		
11			3,400		
26			4,000		
8/12	12.7	4.4	4,400	140,000	
21			4,000		
30			5,500		
1944 4/1	13.0	4.6	5,600		— 5/1
11	13.0	4.4	3,800	165,000	
19			4,900		
25	13.0	4.4	7,000		

Diagnosis: Anemia + leukopenia.

Summary.

A report is made on the subjective symptoms and changes in the blood in a group of men engaged in operations with benzene. In 180 examined persons, chronic poisoning was observed 38 times. Acute poisoning was found in the anamnesis of another 61 of the workmen and 81 of them showed no signs at all of acute or chronic poisoning. The blood changes are collected in table 3 and the subjective symptoms in table 5.

References.

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The plasma-protein fractions during the course of the disease in cases of polyarthritis rheumatica.

By

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In few diseased conditions will the doctor derive so much help from the sedimentation rate (SR), as in the rheumatic diseases. It facilitates the diagnosis as well as the study of the course of the disease and, in some measure, indicates the prognosis. Herrman (1924) and Westergren (1926) were the first to study the sedimentation rate in the rheumatic diseases and found that it was raised. As a rule a considerable rise was already noted in the acute cases. Kahlmeter (1926) pointed out that a increased sedimentation rate may be the only remaining symptom of an apparently cured acute rheumatic polyarthritis, and emphasized in this connection that in the treatment of acute polyarthrites the patient should be kept confined to bed pending the normalization of the sedimentation rate. — In some other arthritic diseases, such as *arthrosis deformans*, the sedimentation rate as a rule is not raised (Westergren).

Fåhraeus (1921), whose work forms the basis of modern SR studies, has shown that not only the fibrinogen but also the globulin percentage has an important bearing on the sedimentation rate in experiments where the blood cells have been suspended in different concentrated solutions of fibrinogen and globulin, respectively. — In order to ascertain how the matter stood in the blood itself, Westergren, Theorell and Widström made an investigation on a

large clinical material. They analyzed a series of blood samples from patients suffering from various internal affections in regard to the sedimentation rate and the plasma-protein fractions: fibrinogen, globulin and albumin. When this material was subjected to statistical analysis, they found the following correlation coefficients: SR-fibrinogen $r = 0.82 \pm 0.04$; SR-globulin $r = 0.50 \pm 0.10$; SR-albumin $r = -0.46 \pm 0.10$. There is thus no absolute correlation between the sedimentation rate and the protein fractions. The correlation would perhaps have been better if the fractioning of the proteins in the plasma had been carried on still further. Gordon and Wardley (1943) have in fact recently shown that the sedimentation rate may be low, despite a high fibrinogen percentage in the plasma, if the pseudoglobulin in the plasma had increased at the expense of the euglobulin. The so-called crystal albumin, a carbohydrate-free albumin fraction, apparently increased the sedimentation rate, whilst the serum glycoid tended to diminish it. — When these conditions are studied in the plasma of the blood itself, matters are further complicated by a number of other elements which affect the sedimentation rate in one direction or the other, such as cholesterin, lysolecitin, and the neutral salts.

On the basis of these facts, certain investigators proceeded to study what pathological changes in the plasma-protein fractions [1] were responsible for the raised sedimentation rate in the rheumatic diseases. These investigations — at any rate those in which the technique was quite unexceptionable — are not numerous. Alred-Brown and Munro (1935) found low albumin, but high fibrinogen and globulin values in a good many cases of chronic rheumatic infection. — Davis (1935) made a comparison between the serum-protein fractions from cases of *polyarthritis chronica* and *arthrosis deformans*. In those suffering from the last-mentioned disease, no demonstrable pathological changes in the fractions could be observed. On the other hand, he noted distinct changes of that nature in the cases of *polyarthritis chronica*. There the globulin fraction, more especially the euglobulin, showed a considerable increase. An increase of the fibrinogen, though less marked than that of the globulin, was likewise noted. The albumin percentage was lower than normal. — Schull, Bach and Pemberton (1939)

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[1] The normal values for the plasma-protein fractions are: fibrinogen 0.20—0.40 %, globulin 1.5—3 %, albumin 3—5 %.

made a similar investigation in regard to various arthritic affections. They did not find any change, characteristic of any special group, in the plasma-protein fractions, except in cases of *polyarthritis chronica,* where the conditions, broadly speaking, corresponded with the findings of the above-mentioned investigators.

The Author's Investigation.

The object of the present investigation was to follow the changes in the plasma-protein fractions during the course of the disease in patients suffering from rheumatic polyarthritis and to correlate those changes to the variations in the sedimentation rate.

The material consisted of 45 cases of rheumatic polyarthritis; all of them were patients in the Medical Department of the Karolinska Hospital. In order to obtain, for correlation purposes, as clearcut a material as possible, patients who had been suffering from other diseases in addition to polyarthritis were excluded. All patients were treated, in some way, with chemotherapy, as well as with physical therapy in various forms. — Blood samples were taken on the admission of the patient to the hospital and afterwards as a rule once a week. The determination of the plasmaprotein fractions was made according to the method of Theorell and Widström. The sedimentation rate test was performed according to the method of Westergren.

Results.

The results of the analysis and the principal clinical facts are summarized in Tables 1 and 2. For the sake of perspicuity, it was found desirable not to include in Table 1 all the figures for the protein analyses: instead, the direction of the changes which had occurred during the treatment is indicated, + designating increase, — decrease, and the sign = no change. In the SR column, for example, $40 \rightarrow 9$ shows that the sedimentation rate has been reduced from 40 to 9 mm per hour during the period of treatment; = 36 indicates that the sedimentation rate has remained unchanged at 36 mm. Table 2 gives the results of the individual protein analyses.

The results of the treatment of the different types of polyarthritis are given in Table 3. 67 per cent. of the cases inproved

Table 1.

Case No.	Sex	Age	Duration of disease in years	Fever	Exsudate in joints	Swelling of synovial capsule	Reduction of cartilage	Dule pains	Pains on moving	Days of hospitalization	Salazopyrin (g)	Salazotiazol (g)	Physical therapy	S. R.	Fibrinogen	Globulin	Albumin	Result of treatment
											Polyarthritis chron. sec.							
1	f.	43	25	+	+	+		+	+	177	182			37→ 16	—	=	+	unim.
2	f.	36	12	+	+	+	—		+	35	137		+	30→ 13	=	—	=	im.
3	f.	45	10	+	+	+	+		+	49	132		+	58→ 22	—	+	—	im.
4	f.	38	9	+	—	+	—		+	48	288			30→ 16	=	=	—	unim.
5	f.	64	8	—		+	+			78	260		+	116→ 65	+	+	—	unim.
6	f.	64	7	+	+	+	+	+		29	144			73→ 29	—	—	+	im.
7	f.	54	6	+	+	+	+	+	+	146	60	354	+	=55	=	—	+	unim.
8	m.	53	5	—		+	+	+		59	310		+	53→ 20	—	—	+	im.
9	m.	52	4	+		+	+		+	17	102			=30	=	=	=	unim.
10	f.	37	4	+	—	—	+		+	33	123		+	22→ 31	=	—	+	im.
11	m.	28	4	—	+	+	+	+	+	42	294			35→ 22	+	=	+	im.
12	m.	52	3	—	+	+	+	+	+	30	68			=42	+	+	—	im.
13	f.	66	2½	+	+	+	+		+	26	132			25→ 63	=	—	=	unim.
14	f.	70	2	+	+	+	+	+		36	73	36		=90	+	+	+	unim.
15	f.	67	2	+	+	+	+	+	+	62	96		+	=110	—	—	—	im.
16	m.	37	2	—		+	—		+	17	96			5→ 18	+	=	—	im.
17	f.	36	2	+		+	+	+		20	0			=20	+	=	—	unim.
18	m.	32	2	+		+			+	40	112		+	=10	—	—	=	im.
19	f.	55	1½	+	+	+	+		+	51	255		+	64→ 26	—	—	+	im.
20	f.	53	1	+	+	+	+		+	129	162	108	+	=50	=	=	=	im.
21	f.	12	8m	+	+	+			+	45	3	168		60→118	=	=	=	im.
22	m.	75	?	+	+	+	+		+	116	96		+	42→ 14	—	+	—	im.
											Polyarthritis chron. prim.							
23	m.	54	10	—		+	+	+		28	149			65→ 55	—	—	+	im.
24	m.	45	10	—	+	+	+		+	33	165		+	72→ 26	—	=	+	im.
25	f.	32	10	+	+	+	+	+	+	97	60	60	+	=55	=	=	=	unim.
26	f.	51	8	+		+	+	+		19	114			29→ 40	=	=	—	unim.
27	f.	42	7	+		+	+	+		54	52	55	+	=35	=	=	—	im.
28	f.	34	7	+		+	+	+		144	556		+	40→ 9	+	=	—	im.
29	f.	56	6	+	+		+			60	55	120		=60	=	=	=	im.
30	f.	45	6	+		+	+		+	286	44	306	+	92→ 30	=	=	=	unim.
31	m.	56	4	—		+	+		+	60	75		+	61→ 34	—	—	—	unim.
32	f.	53	4	+	+	+	+			14	70			=40	=	=	—	unim.
33	f.	41	4	+	+	+	+	+		16	55			=22	=	—	+	im.
34	f.	24	2	+	+	+	+	+	+	293	331		+	=26	=	—	=	unim.
35	m.	23	1	—		+	—		+	84	200		+	28→ 10	=	+	=	im.
36	m.	30	½	—		+			+	37	175		+	32→ 17	=	—	—	im.
											Polyarthritis subchron.							
37	m.	52	5mos.	+		+			+	26	126		+	60→ 33	—	=	—	im.
38	f.	40	5 »	+	—	—	—		+	74	303		+	13→ 35	+	=	—	unim.
39	f.	67	4 »	+		+				33	80			65→ 40	—	=	+	im.
40	m.	30	4 »		+	+	—		·	45	190		+	63→ 25	—	—	+	im.
41	f.	60	3 »	+		+			+	92	21			100→ 45	=	=	+	im.
42	m.	43	2 »	+		+	—		+	33	40	90		=25	=	+	=	im.
43	f.	71	1 »	+		+	+		+	65	54	302	+	79→115	=	+	=	im.
											Polyarthritis acuta							
44	m.	41	1w	+	+	+			+	21	39			126→ 21	—	—	+	im.
45	m.	32	1w	+	+	+			+	28	62	102		34→ 10	+	·	+	im.

Table 2.

Case No.	Date	Fibrinogen	Globulin	Albumin	Total-protein
1.	10/4	0.46	2.96	3.86	7.28
	17/4	0.36	3.09	4.16	7.61
	29/4	—	3.25	4.25	—
	8/5	0.37	3.11	4.43	7.91
	25/5	0.36	2.63	4.42	7.41
	7/6	0.43	2.85	4.69	7.97
	9/7	0.35	2.80	4.24	7.39
2.	11/5	0.23	3.01	4.10	7.34
	27/5	0.34	2.58	3.99	6.99
	9/6	0.18	2.28	4.21	6.67
3.	10/3	0.53	2.96	4.30	7.79
	18/3	0.54	3.09	4.13	7.76
	29/3	0.46	3.77	3.67	7.90
4.	8/3	0.46	2.73	4.30	7.49
	16/3	0.46	2.24	4.27	6.97
	27/3	0.41	2.59	3.99	6.99
	7/4	0.44	2.61	4.10	7.15
5.	8/7	0.66	3.32	3.56	7.54
	16/7	0.70	4.07	2.91	7.68
	22/7	0.79	3.88	2.68	7.35
	13/8	0.82	3.89	2.98	7.69
6.	17/5	0.66	3.07	3.15	6.88
	9/6	0.48	2.77	3.63	6.88
7.	23/3	0.55	3.57	3.23	7.35
	5/4	0.34	3.04	3.56	6.94
	13/4	0.55	3.21	3.55	7.31
	20/4	0.49	3.14	3.45	7.08
	30/4	0.31	2.91	3.76	6.98
	6/5	0.47	2.79	3.73	6.99
	20/5	0.43	2.71	3.89	7.03
	1/6	0.36	2.96	4.14	7.46
	15/6	0.50	3.04	3.84	7.38
	28/6	0.43	2.44	4.00	6.87
8.	24/11	0.42	4.27	2.47	7.16
	3/12	0.52	3.30	3.59	7.41
	15/12	0.43	3.79	3.54	7.76
	28/12	0.35	3.72	3.65	7.72
9.	12/10	0.52	2.59	3.16	6.27
	21/10	0.54	2.62	3.95	7.11
	27/10	0.55	2.56	3.95	7.06

(Table 2. Cont.)

Case No.	Date	Fibrinogen	Globulin	Albumin	Total-protein
10.	10/9	0.29	2.79	4.99	8.07
	20/9	0.40	2.73	4.15	7.28
	29/9	0.31	2.55	4.34	7.20
	8/10	0.31	2.47	4.54	7.32
11.	18/9	0.47	3.16	.3.34	6.97
	28/9	0.55	3.46	3.52	7.53
	8/10	0.47	2.96	4.04	7.47
	19/10	0.56	2.95	3.70	7.21
	25/10	0.67	3.01	3.83	7.51
12.	10/3	0.59	2.61	4.76	7.96
	18/3	0.57	2.26	4.61	7.44
	31/3	0.73	2.77	4.19	7.69
13.	9/9	0.56	4.37	3.17	8.10
	18/9	0.51	3.61	3.09	7.21
14.	27/11	0.40	4.24	1.99	6.63
	9/12	0.78	4.39	2.23	7.40
	17/12	0.73	3.50	2.45	6.68
	28/12	0.81	4.47	2.47	7.75
15.	2/6	0.86	5.47	2.36	8.69
	12/6	0.89	4.66	2.48	8.03
	22/6	0.89	4.69	2.42	8.00
	5/7	0.74	4.69	2.63	8.06
	13/7	0.79	4.65	2.55	7.99
	20/7	0.77	4.28	2.54	7.59
16.	13/7	0.39	2.56	3.94	6.89
	20/7	0.45	2.50	3.24	6.19
17.	22/5	0.25	2.19	4.53	6.97
	4/6	0.39	2.21	3.86	6.46
18.	31/3	0.54	2.50	4.52	7.56
	23/4	0.53	2.10	4.65	7.28
19.	10/3	0.51	4.70	2.34	7.55
	20/3	0.46	3.12	3.86	7.44
	30/3	0.38	2.64	3.63	6.65
20.	10/8*	0.62	2.22	3.64	6.48
	20/8	0.46	2.27	3.70	6.43
	27/8	0.55	2.93	3.26	6.74
	3/9	0.45	2.59	3.53	6.57
	14/9	0.58	2.52	3.24	6,34

(Table 2. Cont.)

Case No.	Date	Fibrinogen	Globulin	Albumin	Total-protein
	23/9	0.53	2.41	3.10	6.04
	1/10	0.53	2.38	3.17	6.08
	12/10	0.57	2.38	3.47	6.42
	20/10	0.54	2.08	3.24	5.86
	29/10	0.59	2.26	3.36	6.21
21.	28/11	0.61	5.63	3.22	9.46
	10/12	0.49	4.90	3.06	8.45
	19/12	0.61	4.86	2.93	8.40
	28/12	0.58	5.79	2.23	8.60
	21/1	0.55	5.10	2.91	8.56
	2/2	0.60	5.35	3.11	9.06
22.	2/7	0.59	2.48	3.86	6.93
	10/8	0.47	2.35	4.02	6.84
	19/8	0.56	2.68	3.88	7.12
	27/8	0.49	3.07	3.70	7.26
	3/9	0.44	2.92	3.39	6.75
	23/9	0.41	2.86	3.15	6.42
23.	13/10	0.55	3.28	3.26	7.09
	19/10	0.48	2.79	3.59	6.86
24.	11/5	0.61	3.63	3.46	7.70
	26/5	0.63	3.79	3.73	8.15
	8/6	0.46	3.73	4.30	8.49
25.	8/3	—	3.27	4.03	7.30
	18/3	0.49	3.15	3.87	7.51
	29/3	0.48	3.48	3.58	7.54
	7/4	0.38	2.90	3.70	6.98
	14/4	0.31	2.76	3.69	6.76
	21/4	0.52	3.13	3.77	7.42
	3/5	—	3.03	4.32	7.35
	17/5	—	3.26	3.81	7.07
26.	23/9	0.50	2.94	3.82	7.26
	5/10	0.54	3.52	3.11	7.17
	13/10	0.47	3.01	3.11	6.59
27.	9/3	0.49	3.80	4.14	8.43
	24/3	0.50	3.99	3.45	7.94
28.	12/11	0.28	2.55	5.29	8.12
	6/12	0.36	2.69	4.31	7.36
	31/1	0.39	1.89	4.75	7.03
	7/3	0.35	2.59	3.98	6.92

(Table 2. Cont.)

Case No.	Date	Fibrinogen	Globulin	Albumin	Total-protein
29.	8/9	0.65	3.26	3.03	6.94
	16/9	0.68	3.70	2.27	6.65
	21/10	0.71	3.07	3.26	7.04
30.	6/3	0.48	2.27	4.86	7.61
	16/3	0.51	3.26	3.72	7.49
	26/3	0.48	3.63	3.45	7.56
	6/4	0.52	2.74	3.71	6.97
	15/4	0.35	2.97	3.98	7.30
	27/4	0.47	3.09	3.73	7.29
	19/5	0.54	2.96	3.44	6.94
	29/5	0.49	2.77	3.82	7.08
	11/6	0.54	3.03	3.71	7.28
	21/6	0.49	3.38	3.40	7.27
	2/7	0.50	2.45	4.22	7.17
	10/7	0.52	2.64	4.03	7.19
	19/7	0.47	2.78	3.75	7.00
31.	15/6	0.63	3.59	3.49	7.71
	29/6	0.74	3.90	2.81	7.45
	9/7	0.41	3.28	2.97	6.66
	19/7	0.38	3.08	3.13	6.59
32.	19/10	0.37	4.50	2.87	7.74
	26/10	0.44	4.58	3.54	8.56
33.	4/12	0.58	3.22	3.63	7.43
	12/12	0.46	2.97	3.39	6.82
	18/12	0.50	2.87	4.70	8.07
34.	31/3	0.62	3.64	3.42	7.68
	15/5	0.46	3.40	3.64	7.50
	19/6	0.46	3.73	3.17	7.36
	20/9	0.58	3.09	4.02	7.69
	7/11	0.53	3.07	3.74	7.34
	3/12	0.59	3.19	3.61	7.39
35.	19/3	0.55	3.04	3.50	7.09
	5/4	0.48	3.36	3.84	7.68
	12/4	0.36	3.48	3.72	7.56
	19/4	0.37	2.76	4.45	7.58
	28/4	—	2.82	4.51	7.33
	7/5	0.48	2.75	4.15	7.38
	24/5	0.47	3.39	3.88	7.74

(Table 2. Cont.)

Case No.	Date	Fibrinogen	Globulin	Albumin	Total-protein
36.	5/5	0.48	2.92	4.49	7.89
	19/5	0.44	2.52	4.39	7.35
	31/5	0.48	2.54	4.19	7.21
	9/6	—	—	4.27	7.93
37.	23/8	0.60	2.89	4.51	8.00
	30/8	0.56	2.80	4.16	7.52
	7/9	0.50	3.07	4.04	7.61
38.	6/9	0.41	3.05	3.98	7.44
	15/9	0.28	2.08	4.62	6.98
	25/9	0.34	1.66	4.73	6.73
	4/10	0.30	2.05	4.58	6.93
	11/10	0.39	2.21	4.27	6.87
39.	17/8	0.74	3.82	2.90	7.46
	26/8	0.55	3.41	2.94	6.90
	2/9	0.58	3.13	2.84	6.55
	13/9	0.42	2.71	3.41	6.54
40.	10/5	0.60	3.66	3.74	8.00
	25/5	0.56	3.52	4.09	8.17
	5/6	0.59	3.82	3.83	8.24
	17/6	0.36	2.71	4.42	7.49
41.	24/9	0.87	2.68	3.74	7.29
	2/10	0.84	2.69	3.41	6.94
	9/10	0.87	2.77	3.93	7.57
	16/10	0.84	2.52	4.46	7.82
	25/10	—	—	3.65	7.10
42.	28/5	0.50	2.88	3.60	6.98
	8/6	0.55	3.01	3.62	7.18
	18/6	0.53	3.31	3.82	7.66
43.	31/8	0.56	3.08	2.91	6.55
	11/9	0.59	3.49	2.76	6.84
	21/9	0.53	3.76	2.60	6.89
	30/9	0.53	3.93	2.38	6.84
	9/10	0.56	3.87	2.72	7.06
	18/10	0.52	3.66	2.87	7.05
44.	15/5	0.91	5.18	2.59	8.68
	27/5	0.37	3.74	3.88	7.99
45.	11/3	0.48	3.45	3.40	7.33
	18/3	0.53	2.92	3.89	7.34

Table 3.

Polyarthritis	Improved cases	Unimproved cases	Total
chron. prim.	8	6	14
chron. sec.	14	8	22
subchron.	6	1	7
acut	2	0	2
Total	30	15	45

during the treatment in hospital, whilst 33 per cent. showed no improvement on discharge. It will be seen from the Table that the primary chronic polyarthrites were less amenable to therapeutic treatment than the secondary chronic. The best results are shown by the subchronic cases, but the material is too small to admit of any definite conclusions.
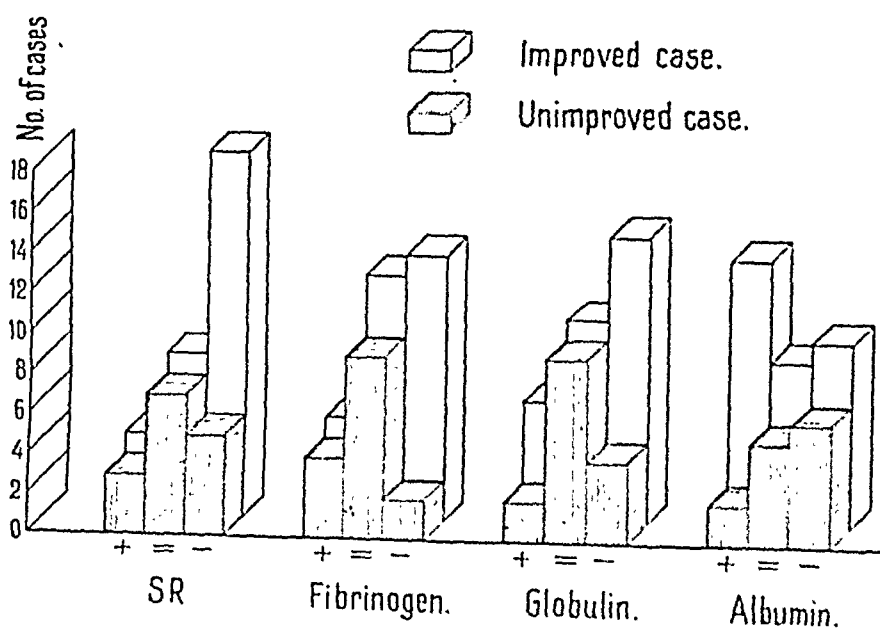
The diagram, which is based on Table 2, illustrates the marked tendency of the sedimentation rate to decrease in the improved cases, though there is no absolute parallelism between this decrease and the clinical improvement. In the unimproved cases no definite tendency in either direction could be noted. — The fibrinogen percentage showed some decrease in the improved cases. Similar conditions were observed in regard to the globulin.

In the unimproved cases there was no definite tendency on these respects. The figures, however, are too small to admit of any far-reaching conclusions. The albumin percentage, on the other hand, increased in the improved cases and apparently diminished in the unimproved.

In Table 2 it will be found that cases Nos. 13, 14, 15, 21 and 32 show a marked increase of the globulin percentage (over 4 %). Nos. 14, 15 and 21 were designated as bad cases with a dubious prognosis. No. 13 had a high globulin percentage from the outset, but it afterwards fell; and, even if the patient had not improved during the treatment in hospital, he showed no serious polyarthritic changes. No. 32, despite a high globulin percentage in the plasma protein, was a moderately severe case. These two last-mentioned milder cases (Nos. 13 and 32) also show merely a moderate rise in the sedimentation rate, whereas in the other above-mentioned cases the rate was markedly raised (about 100).

The diagram thus indicates the *general* tendency in regard to the sedimentation rate and the plasma-protein fractions in improved and unimproved cases. It will be noticed, however, that marked deviations from the usual conditions in these respects may occur in individual cases. For example, in case No. 5 the sedimentation rate fell from 116 to 65, whereas the fibrinogen and globulin percentages increased. The patient showed no improvement during the period of observation, whence the plasma-protein fractions give a truer indication of the state of the disease than the sedimentation rate. — Case No. 30, in spite of a decrease in the sedimentation rate from 92 to 30, showed no improvement in health on discharge; here the plasma-protein fractions were unchanged. — In case No. 11 the sedimentation rate diminished parallel with the improvement in health, whilst the fibrinogen percentage increased and the globulin percentage was unchanged. The same remarks apply to case No. 28.

As previously pointed out, the sedimentation rate is of great importance in studying the course of the disease in cases of rheumatic polyarthritis. There is, however, no absolute parallelism. Its magnitude, as we know, mainly depends on the concentration of the coarsely dispersed proteins in the blood plasma, and it is this fact that has given the sedimentation rate its indubitable value in diagnostics. However, as there is no absolute correlation between

the sedimentation rate and plasma-protein fractions, a truer indication of the gravity of the disease will undoubtedly be given by an analysis of the protein fractions in the plasma. As shown by Table 2, in the great majority of these cases the fibrinogen percentage is raised; and this rise may be maintained even after a reduction in the sedimentation rate and an improvement in the clinical picture. In regard to the exact signifiance of this fact, it is difficult to make a definite statement. Presumably it indicates that the disease is not completely healed, and that the source of infection may still be present, though not demonstrable in any other way. Possibly the tendency to relapse is greater in such cases. This, however, is a question the determination of which must be deferred pending continued control of the patients.

In the statistical elaboration of the material, the same procedure as that of Westergren, Theorell and Widström was adopted. It was found that the correlation coefficients broadily corresponded with those obtained by the said authors. They were for SR-fibrinogen r = 0.82 . 0.03; for SR-globulin   r = 0.48 ± 0.08; and for SR-albumin r = —0.51 ± 0.08.

Table 4.

Correlation coefficients	Westergren, Theorell and Widström	Own researches
SR-fibrinogen	0.82 ± 0.04	0.82 ± 0.03
SR-globulin	0.50 ± 0.10	0.48 ± 0.08
SR-albumin	—0.46 ± 0.10	—0.51 ± 0.08

Thus, in this homogenous material of *polyarthritis rheumatica* cases, the correlation of the sedimentation rate to the plasma-protein fractions did not deviate from the results obtained by the said authors in the treatment of their heterogeneous material.

This investigation thus shows that the sedimentation rate and the plasma-protein fractions are, broadly speaking, normalized in *polyarthritis rheumatica* patients who have clinically improved during the hospital treatment; but that there is no absolute parallelism between these factors and that, in judging the course of the disease, it is important to follow the variations in the plasma-protein fractions.

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From the Surgical and Medical Departments of the Næstved County Hospital (Chiefs: H. Tonnesen and S. A. Holbøll) and the Pathological-anatomical Institute of the Gentofte County Hospital (Chief: A. Søeborg Ohlsen) Denmark.

Arterial Hypertension — Nephrectomy.

By

R. MOVIN, A. SØEBORG OHLSEN and A. MILHOLT PEDERSEN.

After the publication of Goldblatt's studies on experimentally produced hypertension (1928) a number of papers have been published, dealing with experimental and clinical aspects as well as statistical, chiefly by American authors.

In Sweden this problem has been dealt with by Ask-Upmark (Nord. med. *7:* 472, 1942 and *8:* 552), by Euler (Nord. med. *16:* 634, 1943), and by Euler & Sjöstrand (Nord. med. *18:* 1025, 1943).

The first case published in the Scandinavian countries was reported from Denmark by Holten (Ugesk. f. Læger, *24:* 644, 1942) and in a paper by the same author (Nord. med. *28:* 2119, 1941).

Further, reviews of this subject have been given by Bing (Læge-foreningens Aarbog, 1941), T. Hilden (Ugesk. f. Læger, *24:* 633, 1942) and by K. Hilden (Ugesk. f. Læger, *24:* 639, 1942).

Finally, Raaschou has reported a couple of cases (Nord. med. 6: 207, 1943), and also by Hanssen & Wahlgren (Nord. med. *23:* 1037, 1944).

The reviews, as well as Raaschou's paper, give a comprehensive list of literature, and for surveys they are rather exhaustive. On this account, we beg to refer the reader to these publications for such data, and we shall limit ourselves to giving an account of our own case and the considerations occasioned by it.

The case to be reported here was that of a boy, six years old, in which the outstanding data are:

1. A positive history of urinary infection.

2. Albuminuria and subjective symptoms of hypertension.

3. Typical and dangerous hypertensive crises (blood pressure 240/130) during his stay in hospital.

4. Examinations indicating a unilateral kidney lesion.

5. Practically immediate recovery after nephrectomy.

6. Histological picture of a typical pyelonephritic small granular kidney with severe changes in the arterioles.

As the observation period after the operation is over one and a half years, and because the findings are so clear cut just on account of the fact that the patient is a child who is not suffering from any other lesion whatever, it seems reasonable in this case to arrive at some definite, rather important, conclusions in favor of the Goldblatt theory concerning renal hypertension. Furthermore, the case of this boy illustrates that complete recovery may be obtained when treatment aimed at the cause may be instituted at a not all too late point of time. And this is the reason for the publication of this report.

Case History.

Boy, born on 13/2/36. (Surgical Reg. No. March 49/43; Med. Reg. No. 856/42). Admitted on 10/9/42 to the Surg. Dep. (Epidemic Section) for acute anterior poliomyelitis.

Family History. — The parents are well. There is no disposition in the family to kidney disease, hypertension or tuberculosis. Among the 40 members of the family investigated (covering 4 generations) no instance of increased blood pressure is known at all. In the entire family, only one person has died from »heart failure». The entire family is extraordinarily healthy and vital.

Past History. — The child was born at term, by natural delivery. He had an attack of whooping-cough in January 1941. Otherwise he has never had any infectious disease, especially neither scarlet fever nor diphtheria.

Present illness. — When the boy was about 18 months old, the parents observed blood in his urine, but apart from this he presented no symptoms of any illness; and no fever was observed.

The family physician was consulted and he has obligingly furnished the following data: No fever at the examination, nor any oedema. Urine:

+ albumin, + pus, + blood. Microscopy of the urine, 10 days later, show-
ed: No red blood cells; + white blood cells, + hyaline casts. At this time
the blood pressure was 110/60. During the following two years the urine was
examined at intervals of from one to a few months, with alternating + and
0 albumin; no hematuria. In January 1939 microscopy of the urine showed:
0 erythrocytes; + + leucocytes; 0 casts; + albumin. The blood pressure was
90/60. The last examination of the urine, on 3/6/39, showed: 0 alb. After
this, the parents moved to another part of the country, and the urine was
not examined since.

Since then, on the whole, the boy has been well, even though he kept
being somewhat »puny». In May 1941 he was submitted to adeno-tonsillo-
tomy, without any post-operative complications whatever. The blood
pressure was not measured on this occasion.

During the last couple of years he often complained of headache,
mostly in the summer, and especially in the last half of the year (for in-
stance, on excursions he would sometimes say: »Stop! — — or: »My head,
my head!»). Attacks of this kind were largely considered to be »affectation».
These attacks were accompanied by indisposition, but not by vomiting,
dizziness, fainting spells, spasms, or paralysis. Nor, as far as it has been
possible to learn, did he present any eye symptoms. The boy has been
unreasonable and irritable, and for the last half year he has slept but poorly.
No definite heart or pulmonary symptoms have been observed.

The reason for his hospitalization, which took place in the poliomyelitis
season, is the following:

5 days prior to his admission he complained of a very severe frontal
and parietal headache, which subsided in a couple of days. There was no
vomiting. After this, he was feeling well for a couple of days, but during
the night prior to his admission he was again complaining of a very severe
headache and diffuse abdominal pain. In addition, he now commenced
to complain of rigidity of the neck.

Physical Examination:

The boy is thin, slender, rather emaciated, but not particularly exhaust-
ed. His physical development corresponds to his age. No oedema.

Temperature: 37.4°. Pulse: 80.

Distinct rigidity of the neck and back. He is most unwilling to sit up in
bed without the support of the arms; still he is able to do so. No impair-
ment of muscular power or paresis can be demonstrated anywhere. Tonus
apparently normal. All tendon reflexes normal.

Auscultation: No thrill. Borders: C. IV, left sternal margin; ictus in the
5' intercostal space in the medioclavicular line. Action regular = the pulse.
Sounds hammering but clear; P_2 accentuated. No abnormalities in the
lungs.

Abdomen: Normal; no enlargement of the liver or spleen. Kidney
regions apparently normal.

No abnormality revealed elsewhere by the examination.

As the history of the patient gave evidence of a chronic kidney affection, and the boy had complained of headache for a couple of years, his *blood pressure* was measured, and was found to be *170/120, 175/110*. Lumbar puncture was performed at once with evacuation of 15 cm³ of crystal clear spinal fluid under normal pressure. The spinal fluid showed: 55/3 cells (mononuclears); Pandy +; albumin 30; globulin 5; no bacteria.

Distinct rigidity of the neck and back persisted for about 1 week; and these symptoms subsided in the following week. The patient remained free from any paralysis. The temperature rose on the day after admission (morning, 38.6°; evening, 38.4°) but it fell during the following day and kept normal since. The patient stayed in the department for 3 weeks under the diagnosis: Acute anterior poliomyelitis; chronic nephritis. During his stay in this department the blood pressure was controlled regularly and it fell but slightly (see Table 1). The urine, which was examined daily, showed alternatingly 0 and + albumin (0.3—1 mg º/₀₀) granular casts were demonstrated twice. On account of the urinary findings and the considerable hypertension, the patient was transferred to the Medical Department.

Medical Department: 1/10—12/11/1942.

Physical Examination: Same findings as recorded in the Epidemic Dep. The blood pressure was as high as before. With a view to the possibility of stenosis of the isthmus aortae, the blood pressure was taken on the lower extremities, and here it was found to be higher than on the upper extremities, being here 200/120. The intercostal arteries could not be felt.

Roentgenography of the kidneys and urinary passages (indirect pyelography) showed on two examinations: *Normal pyelogram on the left side; failure of excretion on the right side.*

After this, cystoscopy and direct pyelography were performed. The cystoscopy showed normal conditions, the orifices of both ureters appeared normal. It was practically without any difficulty to introduce a ureteral catheter of small caliber (6—7 cm) on the right side. No urine was evacuated through this catheter. Then 5 cm³ of a contrast substance was injected through this catheter but it was not possible to obtain any pyelogram, as all the contrast substance at once oozed down into the bladder. During the first hours after this examination the patient presented no particular symptoms, but hardly 6 hours after he felt poorly, vomited, and suddenly he became markedly unconscious, having shortly after persistent universal tonic and clonic convulsions. The *blood pressure* rose to *240/130.*

His case was now interpreted as an acute attack of hypertensive encephalopathy, and venesection was performed with evacuation of 250 cm³ of blood; in addition he was given 15 g of chloral hydrate, and later, 10 g.

The convulsions ceased after 3 hours. At that time the blood pressure was 170/100. The unconsciousness lasted 10 hours, and when he woke up, he was feeling relatively well, complaining merely of headache. But 13 days later he had a quite similar attack, and this was the first of its kind which apparently occurred without any particular provocation. He be-

came deeply unconscious and had again universal tonic and clonic convulsions, while his blood pressure rose to 210/120. He was again treated with chloral hydrate and the convulsions ceased after one hour, whereas he remained unconscious for 8 hours.
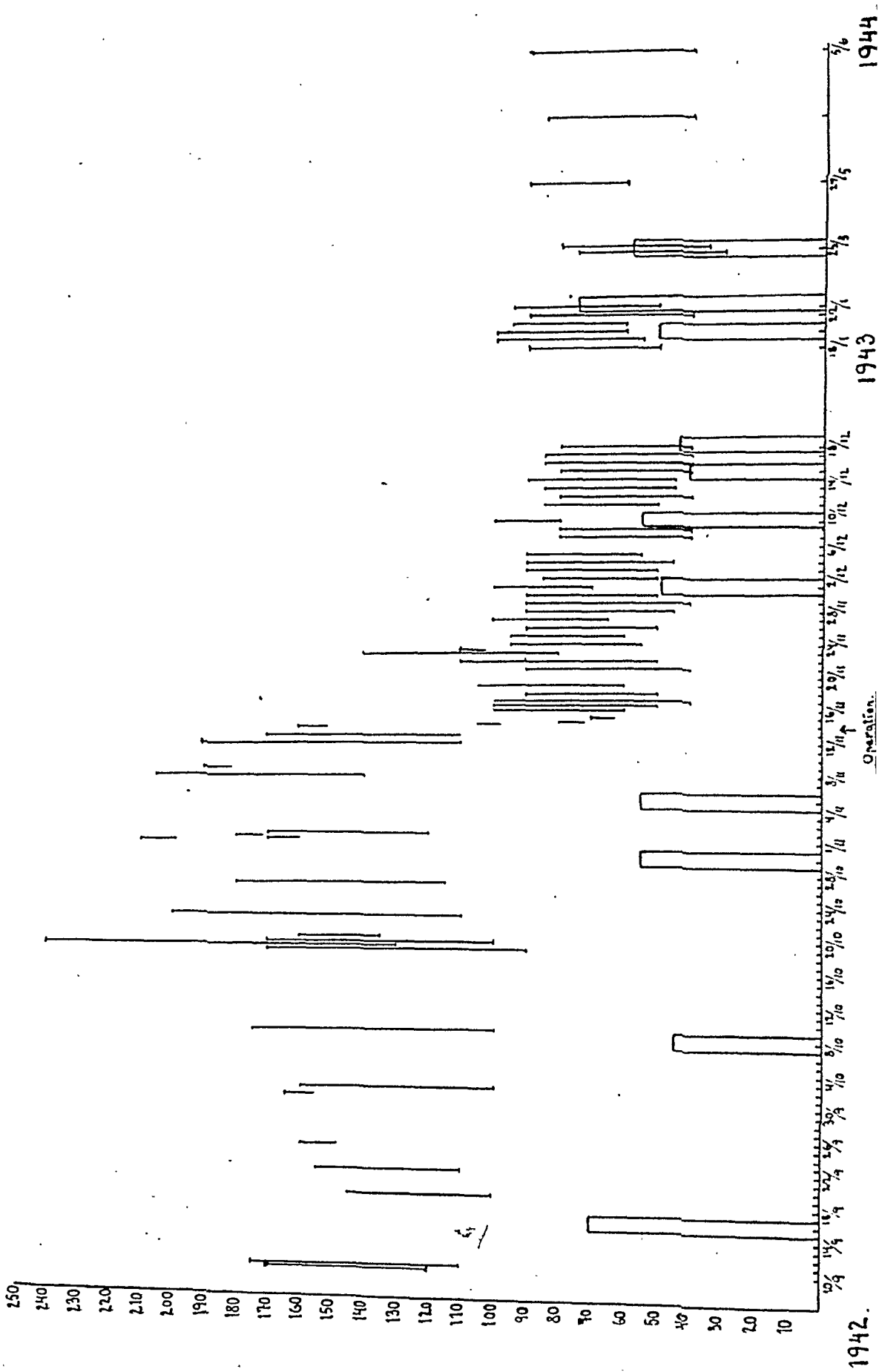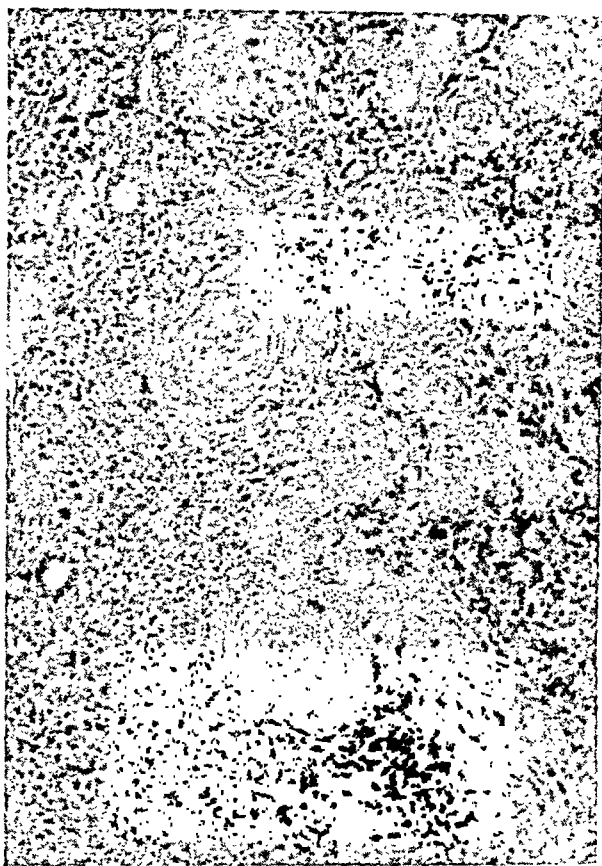

Fig. 1. Section from the kidney removed. Magnif. × 100.

Once more, 10 days later, there was an approach to a hypertensive crisis, as he became restless, whining and later drowsy with twitchings in the arms. Now the blood pressure was 205/140. Lumbar puncture was performed, with evacuation of 15 cm³ of clear spinal fluid, in lively sequence of the drops. After this, deep sleep. The spinal fluid contained 17/3 cells; albumin 90; globulin 7.

Other Examinations:

Microscopy of the urine, which was performed many times, showed only twice a few leucocytes, twice a few granular casts, and otherwise no abnormality. Cultures from catheterized urine showed no growth.

Clearance test (max.): See Table 1.
Blood urea, five examinations: 18—27 mg %.
Strauss concentration test: Concentrations for 1033 to 1020.
Roentgenography of the skull: No abnormality.
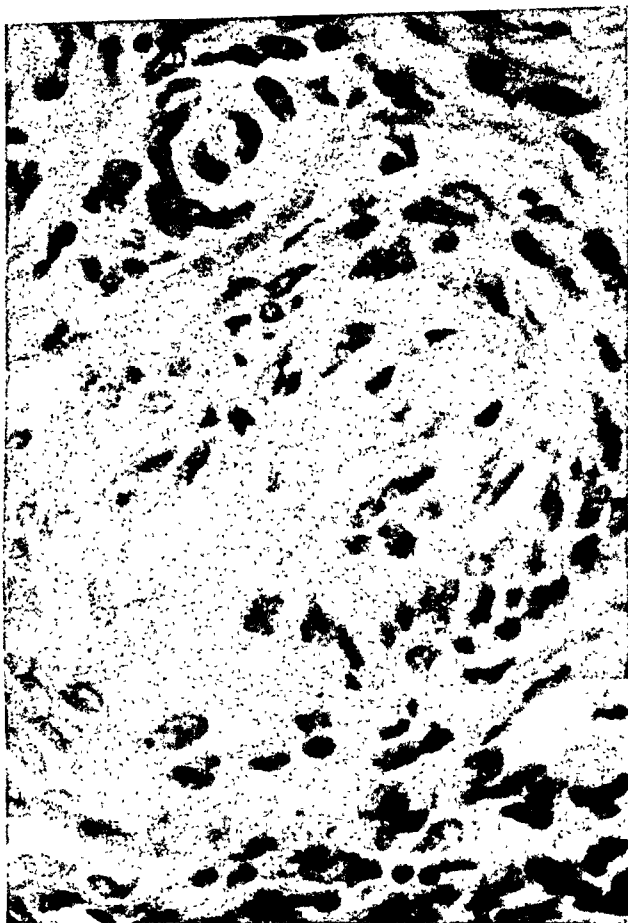
Fig. 2. Hyperplastic arteriole in the kidney removed.   3.   Magnif. × 400.

Roentgenography of the heart and lungs: No abnormality.
Electrocardiography: Normal findings.
Ophthalmoscopy, 8/10: Normal findings.
Glucose tolerance test, 20 g: Fasting blood sugar 0.070 %; maximal
rise after 1 hour to 0.125; with return to 0.070 %, after 2 ½ hours.
Serum chloride (day before the operation): 290 mg %.
Alkali reserve (day before the operation): 44 vol. %.
Weight: 20 kg.
Height: 126 cm.
Hemoglobin: 112—101 %.

Sedimentation rate, 22/9: 4 mm.; after this < 4 mm.
Throat culture: 0 diphtheria bacilli.
Wassermann, in blood: Negative; in spinal fluid: Negative.
Tuberculin test, Mantoux (I—III) negative.
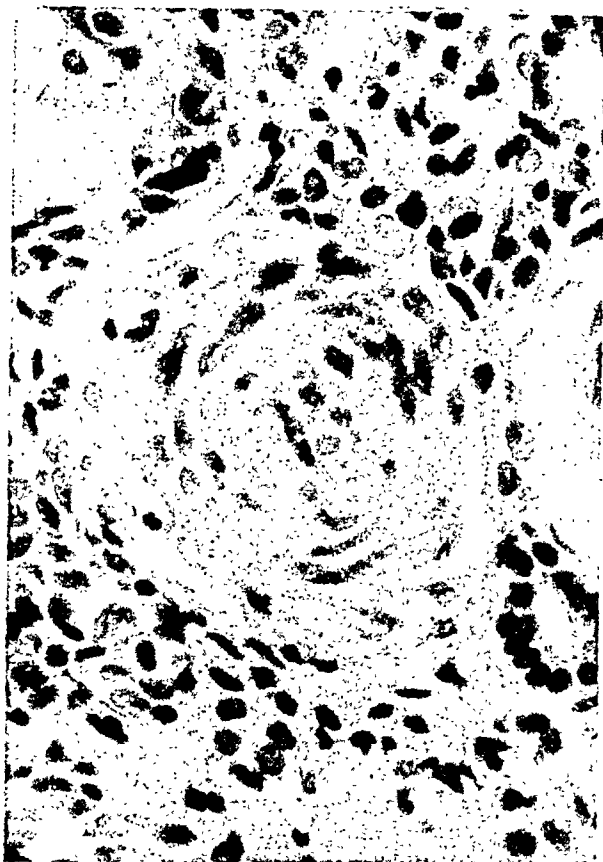
Fig. 3.   Hyperplastic arteriole in the kidney removed.   3. Magnif. × 400.

On account of the history of the patient, the urinary findings and the pyelograms, it seemed reasonable to assume that the hypertension of this case was due to a kidney lesion. The good excretion of the contrast substance on the left side, together with the normal pyelograms on this side and the good results of the functional kidney tests were highly suggestive of the lesion being unilateral.

There were no signs of Cushing's disease, hyperthyroidism or of aortic coarctation. The patient has not presented the typical symptoms of chromaffin adrenal tumors: brief attacks of violent tachycardia, shaking, anxiety, grayish colour of the face, and swelling of the neck. Perirenal

insufflation of the air with roentgenography was considered, but desisted from, as the general condition of the patient gradually had become rather exhausted after the aforementioned 3 crises. His appetite was poor, he was losing weight, and his blood pressure had a distinct tendency to increase.

As nephrectomy was considered to be the only chance of recovery for the patient he was again transferred to the

Surgical Department.

On 14/11/42, under nitrous oxide — oxygen — ether anesthesia, lumbar incision was performed on the right side, with

nephrectomy

(Chief-surgeon Hans Tønnesen).

The right kidney was found to have undergone marked pathological changes. The ureter was normal. The kidney was removed easily and quickly, and palpation of the corresponding adrenal revealed no abnormality, especially no evidence of any tumor.

The boy suffered no shock under the operation, and the blood pressure which has been watched continuously has kept at a level of about 160 mm. The removed kidney was markedly shrunken, of pyelonephritic type. It was sent to Søeborg Ohlsen, Chief Pathologist, for histological examination. In conclusion of this paper Søeborg Ohlsen will give an account of the macroscopic and microscopic changes observed.

Postoperative Course:

The boy was not exhausted by the operation. One hour after the operation the blood pressure was 105 mm (systolic) and in the evening 80 mm. During the rest of his stay in the hospital the blood pressure was measured daily and found to be between 80 and 110 mm systolic and 40—70 diastolic. Once, however, 9 days after the operation, a blood pressure of 140/80 was measured, but in the evening of the same day the systolic pressure was again 110 mm (cf. Table 1). *Since then, the boy has been under observation for more than 18 months, and the systolic pressure has never exceeded 100 mm.*

As early as 4 days after the operation the patient was doing very well, and he felt perfectly well during the rest of his stay in the hospital, and he has done so since. His complaints are all gone, he is not troubled with headache any more, and he is gaining weight. There has been no albuminuria since the operation.

Besides his blood pressure, we were greatly interested in his kidney function. The clearance value kept being fairly nice, but hardly as good as prior to the operation, as now it varied between 41 and 55 cm³ (output of urine per min. from 4.3 to 6 cm³) but subsequent reexaminations have shown normal values. With one exception the Strauss concentration test has shown a good capacity for concentration (up to 1022).

After the operation there was a pronounced oliguria (90 cm³ in 36 hours). On the day after the operation examination of the blood showed: Blood urea 100 mg %; serum chlorine 225 mg %; and alkali reserve 58 vol. %. He was then given glucose saline, and 4 days after the operation the values were again normal and have stayed normal since. The diuresis improved after 36 hours and has kept normal since. Other postoperative examinations:

Spinal fluid: 0/3 cells, albumin < 10, globulin < 1.
Hemoglobin: 87—89 %.
Serum protein: 6.3 %.
Electrocardiogram: No abnormalities.
Ophthalmoscopy: No abnormalities.

Re-examinations.

Examinations in January, March, May and July 1943, and in June 1944 showed:

1. Feeling perfectly well; in particular, never headache. No abnormal urinary phenomena.

2. Blood pressure never over 100 mm, systolic (see Table 1).

3. At all examinations the urine was free from pathological elements.

4. Maximal clearance on 20/1/43: 50 cm³; on 23/1: 75 cm³; and on 25/3: 58 cm³.

Strauss concentration test: 1025.

5. Indirect pyelography in January and March 1943. Good excretion, and normal configuration of the pyelogram.

6. Electrocardiography and ophthalmoscopy in January 1943:

Normal findings.
Hemoglobin: 85—90 %.
Sedimentation rate: 6 mm.

Discussion.

As often emphasized by Bloch, frequently the study of diseases in children gives the best and most reliable information about the morbid conditions.

In the American literature the cases of hypertension of urological nature in unilateral kidney lesion, have been elucidated most fully in younger patients, and the favorable effect of nephrectomy has been indisputably most often in the younger patients.

The same applies to our patient. His hypertension was still of such an early date, his organism still so resistant, and the tissues still so elastic that no permanent morbid changes had yet appeared — particularly in the other kidney, in the vascular system and in

the brain, and thus the proper time for permanent recovery by causal therapy (nephrectomy) had not been missed.

How long his hypertension has persisted is unknown but he has presented symptoms of it for a couple of years, and these symptoms were accentuated during the last half year.

The patient presented several peculiar phenomena which gave rise to various considerations.

Whether he has had poliomyelitis cannot be established with certainty, but the diphasic course, the rigidity of the neck and back, the spinal fluid changes and the brief fever correspond clinically quite to the diphasic form of aparalytic poliomyelitis. Finally, his admission to the hospital took place in the poliomyelitis season. At this point of time the patient presented no sign of hypertensive encephalopathy.

The symptoms of hypertensive crisis did not appear till 6 weeks after the onset of the symptoms for which he was admitted, i.e., at a point of time when it was reasonable to expect that his spinal fluid changes associated with aparalytic poliomyelitis would have subsided. It is reasonable, therefore, to think that the marked spinal fluid changes (17/3 cells; albumin 90; globulin 7) observed during the convulsive attacks have been produced by the hypertensive crisis.

Another phenomenon is the pronounced oliguria during the first couple of days after the operation, when the blood pressure at once fell off to a normal level. At the same time there was a corresponding increase in blood urea and a slight decrease in the values for the kidney function during the first days after the operation. Presumably these findings are attributable to the greatly lowered renal filtration pressure.

The blood pressure was normal as early as one hour after the operation, which is very soon (in the experimental studies by Goldblatt it took about 6 hours, after the nephrectomy before the blood pressure became normal). As apparently the boy suffered no shock, it is reasonable to assume that the fall in blood pressure was due to a decrease in the pressor level of the blood. But, of course, a slight state of shock cannot be excluded as a contributory cause.

In our opinion, it is an interesting fact that the first attack of acute hypertensive encephalopathy occurred in connection with

the introduction of a ureteral catheter on the side affected (6 hours after). To us there is no doubt that this attack was induced through irritation of the efferent urinary passages (cf. hypertension at the presence of a ureteral concretion). So, in this case, we think we meet with three strong arguments in favor of urological hypertension in a unilateral kidney lesion:

1. Complete recovery through nephrectomy.

2. Acute attack of hypertensive encephalopathy in connection with irritation of the ureter on the side affected.

3. The microscopic changes (see below) with pronounced changes in the arterioles — quite similar to those following an experimental hypertension and in malignant nephrosclerosis.

Histological findings.

First the original report on the specimen will be given, then some supplementary remarks concerning the findings.

The kidney measured $7 \times 3 \times 1$ cm. The layer of kidney tissue was very narrow. The fibrous capsule was strongly adherent. On the middle of the convexity there was a scar-like, shrunken area where the renal tissue was particularly scanty, the rim of tissue measuring nearly between 0.50 and 0.75 cm. The tissue was brownish in color and very firm. The macroscopic picture of the specimen with the adherent capsule and the somewhat granular non-uniform surface corresponded mostly to a pyelonephritic shrunken kidney. The pelvis and calyces were ectatic; the ureter left the pelvis at a rather high level.

The mucous membrane of the pelvis and calyces was pale. No tissue that might correspond to parts of the adrenal was found in the perirenal tissue, nor did the microscopic examination demonstrate any adrenal tissue.

The various b'ocks of tissue from the specimen show that the capsule of the kidney is thick, consisting of concentric layers of connective tissue, poor in cells, with areas of hyalinization. In the cortex, most sections show masses of hyalinized small glomeruli, sometimes surrounded by thick fibrous capsules. In such areas the convoluted tubules are ectatic, lined with an atrophic epithelium. The lumina are filled with a homogeneous coagulate. No distinct border can be made out between the cortex and the medulla. The

straight tubules are atrophic and reduced in numbers. The interstitial is increased, in the cortex as well as in the medulla, and infiltrated with a large number of lymphocytes and fewer polymorphonuclear leucocytes and plasma cells. Between these areas of pronounced atrophy, and inflammatory infiltration, islands of kidney tissue are seen in which the glomeruli and tubules are of almost normal character, and in which the inflammatory infiltration is only slight. The ectatic calyces and pelvis are lined with a thin or slightly thicker transitional epithelium of ureteral type. This epithelium is resting on a layer of fibrillary connective tissue that is infiltrated with several polymorphonuclear leucocytes, plasma cells, and lymphocytes.

In some places in the kidney tissue the lymphocytes are accumulated in heaps.

A particular feature of this specimen is the occurrence of markedly changed arterioles in the shrunken areas. Owing to the shrinkage, the number of arteries per unit of tissue is greater than otherwise. The walls of the arterioles are greatly thickened, and this thickening is due both to an increase in the intima and also to an increase in the media.

The lumina of the arteries are very narrow. The changes are seen both in the sublobular arteries and in the afferent vessels. This thickening of the arterioles explains the hypertension observed.

No tissue reaction as in tuberculosis is seen.

Microscopic Diagnosis: Hydronephrotic, pyelonephritic, shrunken kidney with severe hyperplastic changes in the arterioles.

As is evident from this report, the specimen was a typical pyelonephritic shrunken kidney, though complicated with a moderate degree of hydronephrosis. The process in the kidney showed signs of progression. The condition of pyelonephritis was indicated by the inflammatory changes in the mucous membrane of the pelvis and calyces and also by the pronounced interstitial, though varying, inflammatory infiltration, proliferation and fibrous changes in the kidney parenchyma. According to Soma Weiss and Fr. Parker, jnr, ectatic atrophic tubules with colloid casts are particularly characteristic of pyelonephritis, and such features are described in this specimen. The glomerular changes were mostly of degenerative nature, but also glomeruli with thick fibrous

capsules were found — a feature that is quite in keeping with pyelonephritis. The most interesting feature of the preparation, however, was the arteriolar changes. The arterioles, the sublobular, as well as the afferent, were very thick-walled, and this thickening was due to a concurrent hyperplasia of the fibrocellular elements of the intima and of the smooth muscle layer of the media. One of the hyperplastic arterioles showed also inflammatory infiltration. Here and there also the arteries showed focal thickening of the intima and elastic hyperplasia. These changes in the arterioles correspond to the findings described in malignant hypertension — except that in this case there has not been demonstrated any necrosis of arterioles with hemorrhage. According to Goldblatt, as well as to Soma Weiss and Fr. Parker, jnr., it takes more than hypertension to produce this change, namely: considerable renal insufficiency with uremia.

How do these arteriolar changes appear in pyelonephritis? Here I am inclined to subscribe to the probable explanation offered by Soma Weiss and Fr. Parker, jnr.: The inflammation sets the proliferative arteriolar changes a-going. The resulting narrowing of the lumina brings about ischemia of the kidney tissue, and thus hypertension is induced through an increased output of renin. Thus a vicious circle is established between the inflammation which elicits the arteriolar hyperplasia and the hypertension which accentuates this hyperplasia. The production of hypertension by unilateral pyelonephritis speaks in favor of the correctness of this view. Furthermore, the most severe arteriolar changes are seen in the areas presenting inflammatory infiltration. It is quite correct, then, to associate these severe arteriolar changes with the hypertension.

Summary.

The authors report the clinical course and the histological findings in a case of hypertension due to unilateral kidney lesion in a child.

This is the case of a boy, 6 years old, who at the age of 18 months was suffering from an infection of the urinary passages. During the following years he had periodical albuminuria.

For the last two years he has often complained of severe head-

aches. He was hospitalized on account of an assumed attack of acute anterior poliomyelitis, which took an aparalytic course.

The clinical examination revealed a considerable and stationary increase in the blood pressure (175/110) and albuminuria.

Pyelography and functional kidney test showed the affection to be unilateral.

Ureteral chatheterization was followed by a violent attack of hypertensive encephalopathy, with a blood pressure of 240/130; and subsequently there were two similar dangerous attacks.

Nephrectomy was performed, and one hour after the operation the systolic blood pressure was 105; and it has been normal since. He has been under control observation now for more than 18 months after the operation, and he has been perfectly free from symptoms.

Microscopic examination of the kidney showed hydronephrosis, pyelonephritis, shrinkage of the kidney, with severe hyperplastic arteriolar changes.

Discussion of the case is given.

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Riboflavin and Aneurin Excretion in Coeliac Disease.

By

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In recent years, in the discussion of the etiology and patho-
genesis of coeliac disease, vitamin B_2 (riboflavin) has occupied a
conspicuous place. All authors agree that coeliac disease may be
associated with symptoms suggestive of vitamin B_2 deficiency.
But the point of dispute is whether such an avitaminosis is to
be classified together with the other secondary avitaminoses
encountered in coeliac disease or whether a primary pathogenetic
or etiological significance is to be attached to the vitamin B_2 defi-
ciency. In particular, the studies reported by Verzár (11) has lent
considerable support to the latter view.

According to Verzár, some substances are absorbed in the in-
testine through simple diffusion and osmosis, whereas others ―
including riboflavin and aneurin are absorbed far more rapidly
through an active cellular activity connected with the process of
phosphorylization, the so-called »selective» absorption. With
disturbances of this process the riboflavin and aneurin are not
transformed to their active phosphoric acid compound, and the
result is the appearance of avitaminoses B_1 and B_2. In analogy with
the »experimental Gee-Herter's disease» produced in rat by extir-
pation of the adrenals or chronic poisoning with monoiodo-acetic
acid, Verzár claims that coeliac disease is associated with a disturb-

ance of the selective absorption produced by B_2 avitaminosis that has been brought about by a primary adrenal insufficiency.

Verzár's work and hypotheses have been criticized severely and opposed [Marazzi & Gaunt (8), 1939; Bruce & Wien (2), 1940; Clarke 1941), and the question cannot be said to have been settled yet.

The clinicians refute all theories about the primary adrenal etiology in coeliac disease, whereas some authors [Rietschel (9) Hansen (7)] do not venture to exclude the possibility that vitamin B_2 deficiency may play some role in the disturbances of the absorption.

Dubois (4) has tried to apply the theories obtained by Verzár from animal experiments to man and to show that a primary disturbance of selective absorption was present in coeliac disease. With the support afforded by reports of favorable therapeutic results from administration of vitamin B_2-containing preparations and, especially, on the basis of his own findings concerning the excretion of riboflavin in coeliac disease, he arrived at the conclusion that the B_2 avitaminosis observed by him is the most probable cause of the absorptive disturbance, but he fails to enter into the details in this connection.

With the standard tolerance test suggested by himself in 2 cases of coeliac disease and 1 case of idiopathic steatorrhea (a lesion in adults considered identical with coeliac disease) Dubois found a constant fundamental and serious disturbance of the absorption of riboflavin, possibly due to a change in the selective absorption.

Vanotti (10) (1940) found a considerable lactoflavin deficit in sprue (no data given). In several cases of steatorrhea Antognini (1) (1941) has been able by parentheral administration to demonstrate the presence of a B_2 avitaminosis which he considers secondary to the absorptive disturbance.

We have tried, therefore, whether by determination of the riboflavin and aneurin output in the 24-hour urine of patients with coeliac disease it might be possible to demonstrate a decrease in the spontaneous diurnal excretion of these substances, and in tolerance tests we have tried whether it might be practicable to demonstrate a lowered excretion as an expression of lowered absorption or increased retention.

Experiments were carried out in the Pediatric Department of the Rigshospital, to which 31 patients with coeliac disease have been

admitted during the last two years and where Preben Plum has tried out the treatment with the individual vitamins of the B group in pure preparations and also the various yeast, liver and adrenal preparations together with a low fat and high protein diet. The effect of this treatment has consisted essentially in the absence of the symptoms of deficiency. In the 6 of these patients who were given pure riboflavin, the course of the disease kept varying, so that here there was no improvement of the patients, let alone any recovery.

The riboflavin determinations were carried out after a fluorescence method that will be described in detail in another paper. The urine is adsorbed to an aluminium oxide-floridin column, eluated with a pyridin mixture, and measured, after oxidation with potassium permanganate, in a fluorometer with photocells.

The 24-hour urine is collected for 5—6 consecutive days. The spontaneous excretion is established for two days. Then the test dose of 3 mg riboflavin (after Dubois) is given at 9 o'clock in the morning, by mouth on the 3' day and intramuscularly on the 5' day. For control material we have employed 10 boys of about the same age or weight as the children with coeliac disease; these controls have been normal or suffering from affections which presumably have no influence on the absorption.

The aneurin determination is performed after the thiochrome method as modified by Westenbrink (12, 13); adsorption of the urinary aneurin to franconite, eluation with sodium hydroxide, and oxidation with potassium ferricyanide. The resulting thiochrome is extracted in isobutanol and determined in Cohen's fluorometer. The 24-hour urine is collected for 4 days and the spontaneous excretion is recorded as the average. The test dose of aneurin has been 1 mg given by mouth to the younger patients, 2 mg to the older ones. Between the first and the second tests there has been an interval of 3 days — in order to assure that all the aneurin given in the first dose has been excreted.

The spontaneous excretion in these patients has been compared with the excretion in normal children, partly of the same age, partly of the same weight, after a calculated regression curve for the aneurin excretion in normal children, aged 0—14 years (to be published in another paper).

Table 1.
Riboflavin Output in ,Normal, Children.

No.	Diagnosis	Age in months	Weight in kg	Average spontaneous 24-hour output in γ	Additional output in γ of riboflavin in tolerance tests	
					By mouth	Intra-muscularly
1	Chondrodystrophy ..	13	7.6	405	1122	1006
2	Rickets	7	7.3	589	884	
3	Fract. of clavicle....	9	7.8	488	743	1520
4	Imbecility	21	11.5	442	. 980	1664
5	Bronchial asthma ..	16	13.7	833	961	1319
6	Normal	18	11.5	726	1565	1447
7	Normal	10	11.5	319	743	
8	Normal	15	11.7	360	1078	
9	Adipositas	18	12.5	170		1620
10	Hydrocephalus	11	10.7	383	1968	2293

As to previous studies on the excretion of aneurin in the children suffering from coeliac disease, only one report has been published previously, as far as we have been able to find out: In a patient, 3 years old, suffering from coeliac disease, Gerrits found the aneurin excretion to be normal, i.e., $= 6\%$. The diuresis is not given, and no tolerance test performed.

The patient material comprises 8 boys (boys being preferable with a view to the collection of the urine), aged from 12 to 28 month, and 1 girl, 13 years old. The diagnosis was established by the typical clinical features of the cases together with the characteristic laboratory findings. At the time of these experiments all the patients were at an active stage of the lesion, and all but No. 11 weighed between 2 and 5 kg less than normal for their age. The diet given these children was poor in fat, rich in protein and carbohydrate, with decreased amounts of whole milk.

Every form of vitamin B_2 medicamentation has been discontinued during the experimental period or — when the tolerance test was not performed shortly after admission — 2—3 weeks before the experiment. The outcome of the experiments are recorded in Tables 1 and 2.

From Tables 1 and 2 it is evident that in both groups of children the values obtained for riboflavin are subject to wide variation. In

Table 2.
Excretion of Riboflavin and Aneurin in Children with Coeliar Disease.

No.	Age in months	Weight in kg	Riboflavin in γ			Aneurin in γ		
			Average spontan. 24-hour output	Additional output after tolerance tests		Average spontan. 24-hour output	Additional output after tolerance tests	
				By mouth	Intramuscularly		By mouth	Intramuscularly
11	15	10.8	591	1515	2011	30		
12	8	5.6				27		
"	18	7.5	447	1871	2073	64		
13	20	10.2	291	1103	1791			
14	13	5.5				8		
"	21	6.7	191	930	2130	64		410
15	21	10.0	503	1158	2275	68	47	
16	160	24.8	883	1349	1311	71	167[1]	676[1]
17	28	8.5				23	216[1]	626[1]
18	17	8.2	382	386	1786	11	106	
19	12	5.1	415	451	115	33	11	

[1] Test dose: 2 mg aneurin.

the control group the average spontaneous diurnal output varies between 170 and 833 γ. In the tolerance test with riboflavin given by mouth the 24-hour output is increased by 25—65 % of the given dose, after intramuscular administration by 34—76 %. These values are of the same magnitude as those obtained by Dubois. Among the patients with coeliac disease Nos. 11—16 inclusive form a uniform group, which does not deviate from the control group. No. 18 showed a low output after oral administration of riboflavin, but normal output after intramuscular injection of the substance. Repeated tests with ingestion of riboflavin showed a normal excretion. No. 19 gave low values — strikingly low after intramuscular injection of riboflavin. As subsequent tests with ingestion of the substance showed a normal output, it may be that some technical error was made in the first test.

Naturally a statistical treatment of such a small and non-homogeneous material is of dubious significance, but it has been carried out anyhow. It shows no significant difference in the spontaneous excretion for the two groups or in the outcome of the tolerance tests. In his patients, Dubois found a maximal increase in the output in the tolerance tests amounting to 11 %.

So these experiments show that in most of the cases of coeliac disease here examined there was neither any disturbance of absorption nor retention of riboflavin, and thus they go against the view that riboflavin plays an etiological role in coeliac disease.

As the aneurin excretion with the urine normally depends on the aneurin content of the diet, comparison has been made between the diet of the normal children and that of the children with coeliac disease. The calculation has been carried out after Groth-Petersen's (6) table, and the caloric supply as well as the aneurin intake were found to be the same for the normal children and the patients. Also when the amount of aneurin per 100 cal. was calculated, the figures for the two groups of children were alike except in the case of No. 18. On the other hand, in patients Nos. 14, 16 and 17 carbohydrate was found to constitute a greater percental part of the diet than normally (80—88 % as against 55 %). The 24-hour aneurin output ot these three children was below the normal. Also No. 18, whose diet chiefly consisted in mother's milk, showed an aneurin output below the normal. In tolerance tests with oral as well as subcutaneous administration of aneurin the additional excretion kept within the normal limits. In No. 15 the spontaneous excretion was normal, but in the tolerance tests with ingestion of aneurin the output in Nos. 15 and 19 was lower than normally.

So the results obtained in these experiments are not consistent. The low spontaneous output in 3 of the patients may be explained as attributable to increased requirement of aneurin, as a greater amount of carbohydrate is metabolized by these children. The test dose employed revealed no sign of lowered absorption. With daily intake of aneurin No. 17 showed an increase in the output — just as in normal children. No. 18 received mostly mother's milk, which is stated to contain less aneurin than cow's milk; and this might explain the lower output in this case, as the additional output in the tolerance test here was normal. Whether the low output shown by Nos. 15 and 19 in the tolerance tests be due to poor absorption or to retention cannot be decided.

Summary.

Comparative studies are carried out on the spontaneous diurnal excretion of riboflavin and aneurin, besides the additional output of the substances in tolerance tests per os or intramuscular, in 9 children suffering from coeliac disease and in a corresponding control group. Of the 9 patients 6 presented similar features of ribo–flavin excretion as were found in the controls, while in the tolerance tests 2 patients gave low values for the output, although in subsequent tests the values were not definitely abnormal. In 4 patients the spontaneous aneurin output was lower than normally, but the output in the tolerance tests was normal. In the remainder of the patients the spontaneous diurnal output was normal, while 2 of them showed a lowered excretion in the tolerance tests.

Thus the present studies offer no evidence in support of the assumption that coeliac disease is associated with a disturbance of the absorption of riboflavin or aneurin.

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Electrocardiographic Studies in a Case of Serous Tuberculous Pericarditis in the Initial Stage.

(With Report of the Post-Mortem Findings).

By

L. E. WARFVINGE.

The diagnosis of pericarditis is often difficult. Since it was demonstrated that pericarditis produced changes in the electrocardiogram, major diagnostic value has been attributed to these findings. The first description of these characteristic changes were published about the year 1920. In 1925 Wood and White published a few cases of uremic pericarditis presenting elevation of the S-T segment in all three leads, and Porte and Pardee (1929) observed coronary T-waves in the presence of pericarditis. Differential diagnosis from myocardial infarction, however, encountered great difficulty for a long time, as early investigators confined their reports on nonspecific changes recorded in the presence of pericarditis, namely »low-voltage» and »T-Abflachung». Scott, Feil and Katz (1929) were the first to demonstrate in all leads reciprocal S-T changes which characterize and differentiate the electrocardiograms obtained in the presence of pericarditis from the tracings produced by myocardial infarction. Schwab and Herrmann called attention to the fact that pericarditis, though always producing elevation of the middle segment, never caused depression, and Holzmann stated that, contrary to the condition found in the presence of myocardial infarction, there was absence of marked Q-

changes, if pericarditis was present. If anterior and posterior infarction coexist, elevation of the S-T segments may, however, occur in all three leads, a fact which is due to the summation effect (Wolferth and Wood). But coincident anterior and posterior infarction always produces a marked Q-wave or a pathological chest lead.

Herrmann and Schwab were the first to classify three stages of pericarditis on the basis of the electrocardiographic changes recorded in the presence of this condition, and Holzmann has to be credited for the further elaboration of this classification. Owing to the fact that the electrocardiographic patterns produced by pericarditis, as a rule, follow a regular course, these characteristic changes are of major diagnostical importance. According to Winternitz and Langendorf the different stages of pericarditis as interpreted in the light of the electrocardiographic findings are the following:

Stage I: Arch-shaped elevated take-off of the S-T segment reciprocal in all three leads and low-voltage. In recent pericarditis producing a high take-off of the S-T segment, this and the T-wave form an upright concave arch. These patterns characteristically contrast with the convex high take-off recorded in the presence of coronary thrombosis. This high take-off is never as marked as in the presence of myocardial infarction, and even in severe cases, it never exceeds 0.35 mv. As a rule, it is most pronounced in Lead II and least marked in Lead III. An arch-shaped elevated S-T segment coexisting with a pronounced T-wave suggests the presence of recent pericarditis. At the end of the third week after the onset of the disease, this high take-off usually disappears.

Stage II: Transition to a negative T-wave. The arch-shaped elevated S-T segment is flattened and approaches the iso-electric level. The T-wave may have completely disappeared, but it may also persist in the shape of »kleiner, später Buckel», apparently delayed, while the first phase of the T-wave has disappeared. This is followed by a downward pointing phase. Frequently this phase is visualized in the shape of a negative notch in a persisting T-wave and produces a characteristic »Doppelgipfligkeit». Apart from pericarditis which produces a double T-wave, this pattern is of very rare occurrence. When the negative notch reaches below the 0-level, stage III sets in.

Stage III: Negative T-wave (Pardee-T). In this stage the S-T segment is nearly always deflected towards the iso-electric line. The S-T segment passes into a pointed, negative T which is never as deep as in the presence of infarction. Pardee-T is not likely to be produced earlier than on the 11th day after the onset of the disease, but, as a rule, it is not recorded before the end of the third week. This phase disappears in cases which are cured within periods ranging from one up to several months. If pericarditis is arrested, a definite, pointed, negative T-wave never persists. This characteristic differentiates the patterns recorded in pericarditis from those produced by myocardial infarction.

Stage IV: At first the T-waves are flat, but later become normal. This development takes weeks and sometimes even months and always sets in later than the clinical recovery.

For a long time, the electrocardiographic changes recorded in the presence of pericarditis were considered to be due to cardiac tamponade. Nowadays, however, the assumption may be advanced that the changes in the electrocardiogram are not due to the pressure of the fluid present in the pericardium, but that they indicate the coexistence of myocarditis. A large number of animal experiments have demonstrated that a reversible elevation of the S-T segment may be produced in the electrocardiogram by filling the pericardium with liquid. The same electrocardiographic changes could, however, be produced by simply opening the pericardium. The findings at the microscopical examination made after some time had elapsed, showed in the animals experimented upon, that »inflammation of the epicardium extended into the adjacent myocardium. Degenerative changes were evident in the superficial muscle fibres» (Towler, Rathe and Smith). On the basis of their results obtained with animal experimentation, these authors et al. advanced the view that the electrocardiographic changes in the presence of pericarditis were due to damage of the myocardium.

The same electrocardiographic changes can be produced by chemical irritants. Similar cardiographic changes are clinically also recorded in the presence of dry as well as exudative pericarditis. Myocardial ischemia which may occur, possibly plays a part in producing low-voltage. Transudate in the pericardial sac

which may be of very severe character in cases of heart-insufficiency, and which, doubtlessly, can produce a compression- effect, never causes elevation of the S-T segment provided that the transudate is not of inflammatory character (Azpitarte). In the presence of hematopericardium, however, the electrocardiographic changes may often be interpreted as characteristic of the reaction of the pericardium and may be elicited by the slightest cardiac trauma.

The fact that the electrocardiographic changes frequently are most marked in Lead II may be due to a summation effect, because both the anterior as well as the posterior surfaces of the ventricles are affected to about the same extent. The absence of deeper myocardial changes explains the absence of the Q-wave and of a pathological chest lead.

In the year 1937 Van der Veer and Norris published the results of a careful analysis of 5 cases of purulent pericarditis and of 1 case of haematopericardium. In all cases electrocardiograms were made daily and death occurred at stage I of the electrocardiographic changes. The microscopical examination revealed in all cases signs of subepicardial myocarditis. In 4 cases of pericarditis studied simultaneously and which yielded normal electrocardiograms, no myocardial changes were demonstrable. Of a total of six cases each yielding a »positive electrocardiogram», three did not show any evidence of increased pericardial fluid. Gross variations in the pathologic-anatomical changes were observed. There was evidence of scanty infiltration of leucocytes round the vessels or of cell infiltration round the muscle fibres as well as of edema and of degeneration of the myocardium. These authors had no opportunity of studying a case of serous pericarditis, and they summarize their observations as follows: »If myocardial inflammation is present, it is possible that some cases of nonsuppurative pericarditis would show similar electrocardiographic changes».

Acute serous pericarditis per se is very rarely dangerous to life and therefore death at the inititial stage seldom occurs in cases exhibiting this disease. The observation of such a case illustrating the pathogenetic significance of myocarditis with regard to the electrocardiographic pattern as well as its independence of the pressure caused by the pericardial fluid, appeared therefore of sufficient importance to merit to be reported.

Case Report.

A female, 21 years of age, developed erythema nodosum in July 1942. Roentgen examination revealed lymphomas in the hilum and in the paratracheal region. As the lymphomas extended and fresh one developed on the neck, she was admitted to Solliden Sanatorium in January 1943. In February 1943, she developed a right-sided pleuritis. The guineapig-test with the ventricular fluid was positive. There was a remittent fever fluctuating between 37.5° and 38.5°.

Towards the end of the month of October 1943, pericarditic rales »Lokomotivgeräusch» were heard, and a few days later there was a marked enlargement of the area of absolute cardiac dullness. The fluoroscopic examination 12 days after the onset of the first clinical symptoms revealed that there was dilatation of the pericardium due to a massive exudate. No pulsations were appreciable. The patient complained of a feeling of oppression in the chest and therefore the exudate was tapped. Immediately prior to the paracentesis an electrocardiogram was taken (Fig. 1, A). The pericardial sac was tapped and firstly 250 cm³ of serous, slightly blood-tinged exudate were aspirated, and then the patient was allowed to freely inspire air through the needle until the pressure was 0. Immediately after the removal of the exudate a further electrocardiogram was taken (Fig. 1, B). Four hours later a third record was taken (Fig. 1, C). At the end of twenty-four hours the last electrocardiogram was taken. Following the surgical intervention the patient felt greatly relieved, but 5 days later a violent haemoptysis suddenly set in and death occurred within a few minutes.

The post-mortem examination revealed a dilated cardiac sac containing air and 200 cm³ serous, blood-tinged exudate. Both the pericardium and the epicardium were covered with a loose coating of fibrin which was easily removed by scraping. Solitary thin streaks of fibrin stretched from the pericardium to the epicardium. Macroscopically, no changes within the myo- or endocardium were demonstrable. The haemorrhage causing lethal exit was due to a cavernous process within the right superior lobe. Tubercle bacilli were demonstrated in cultures from the pericardial exudate.

The histological examination of different parts of the heart showed a thickening of the pericardium which was edematous and heavily infiltrated with inflammatory cells, the majority of which were leucocytes. Large amounts of fibrin were present on the surface. *In the underlying myocardium small numbers of inflammatory cells accumulated round the vessels (Fig. 2) and signs indicative of a mild myocarditis were recognized (Wahlgren).*

The electrocardiogram taken about a fortnight subsequent to the onset of the pericarditis (A) illustrates the typical initial stage with low-voltage, slightly elevated arch-shaped take-off of the

A. Prior to paracentesis.
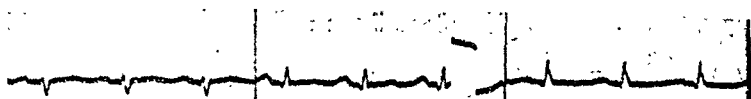
B. Immediately after inspiration of air.
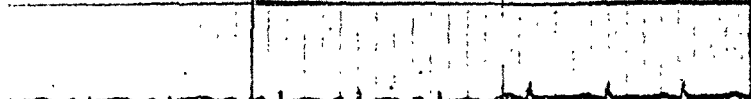
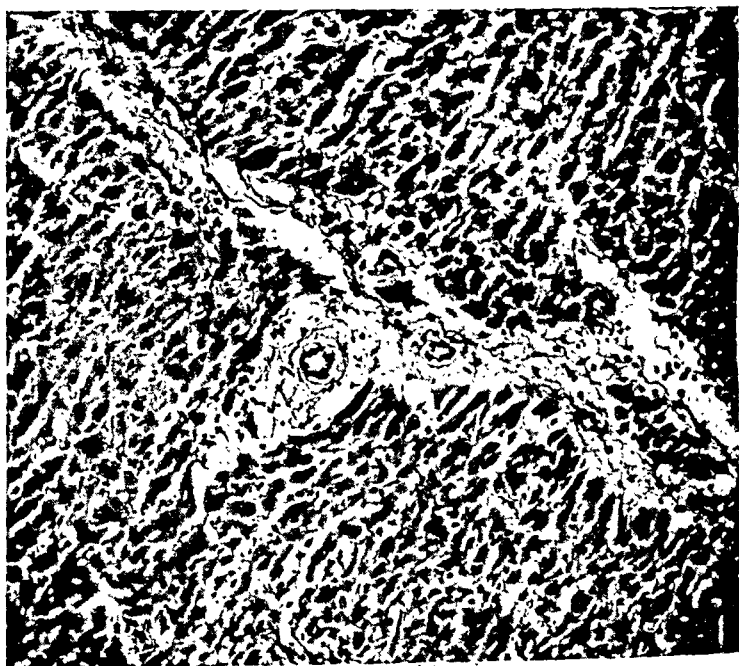C. 4 hours after paracentesis.

Fig. 1.

Fig. 2

S-T segment in Lead I and Lead II, and the coexisting positive T-wave in Lead I and Lead II. With the exception of S_{II} and P being more developed, no other changes were recorded following paracentesis and inspiration of air until the pressure was 0 (B). Four hours subsequent to paracentesis when, owing to the resorption of the oxygen the pericardial pressure was most likely negative, the electrocardiogram showed that S and P were less marked (C). 24 hours later, when the exudate had partly reformed and the pressure was most likely positive, the appearance of the electrocardiogram was exactly the same as before the inspiration of air. In the whole series of electrocardiograms the appearance of the S-T segments and of the T-waves did not change.

So far as the author is aware, no post-mortem findings of a case of serous pericarditis in the initial stage have as yet been published in the literature. The present investigation demonstrates that the fluctuations in the pericardial pressure do not essentially influence the electrocardiogram and that the electrocardiographic changes at stage I of serous pericarditis are due to changes in the myocardium.

Summary.

A case of acute, serous, tuberculous pericarditis is described, exhibiting electrocardiographic changes typical of the initial stage of this disease. The aspect of these changes did not alter paralell with the changes in the pressure occurring in the pericardium subsequent to paracentesis and inspiration of air. The histological examination of the heart made five days later revealed signs of subepicardial myocarditis.

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The Correlation between the RQ Curve and the Blood Sugar Curve after Administration of Insulin to Diabetic Subjects.

By

KNUD LUNDBÆK.

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Administration of insulin to pancreatectomized animals or human diabetics causes a rise of the respiratory quotient (RQ). This fact has been known since the discovery of insulin (Banting, Best, Collip, Hepburn & Macleod, 1922) and has been established by the investigations of Holten (1925).

In an earlier paper (Lundbæk, 1943, 1944), dealing with the effect of insulin on the RQ of normal individuals, a correlation has been demonstrated between the RQ curve and the blood sugar curve. (Fig. 1.) (summation curves of 48 experiments). It was shown that generally, after injection of large doses of insulin provoking hypo-glycemic coma, as well as after small doses (8—24 units), the RQ, values increases only as long time as the blood sugar is falling. When the blood sugar fall ceases, the RQ drops back towards the initial values, despite the fact that a strong insulin action is still present as appears from the persistence of a low blood sugar and the development of hypoglycemic symptoms.

This correlation has been interpreted as follows. During the initial fall of the blood sugar, the outflow of glucose from blood to tissue cells is greatly increased, causing an increase in the percen-
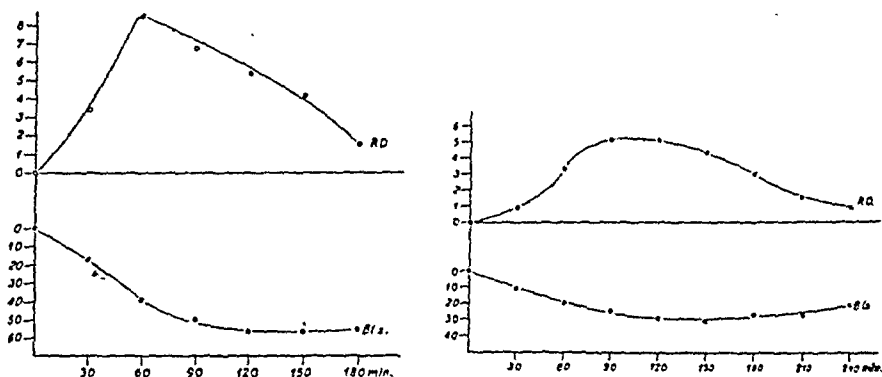
Fig. 1.

Rise in RQ (RQ-units = 0.01 RQ) and fall in blood sugar after large and small doses of insulin to normal subjects.

tage amount of carbohydrates in the total combustion. (Rise of RQ.) When the blood sugar ceases falling, a new equilibrium is established, determined by a higher concentration of insulin and a lower concentration of glucose in the blood. During this new equilibrium the outflow of glucose from blood to tissues is again of the same magnitude as before the injection of insulin, causing the RQ to drop back to the initial values.

The carbohydrate combustion therefore seems related to the *variations* of the blood sugar, not to its actual *level*.

An analysis of the course taken by the RQ curve and its relation to the blood sugar curve in diabetics is not found in the literature. The present communication reports some experiments to the elucidation of this problem.

Methods.

The methods employed have been essentially the same as described in the paper previously mentioned. Ventilation, O_2 consumption, CO_2 production and RQ were determined in 5 minutes periods before and every 30 minutes after injection of insulin. Douglas bags were used for collecting the expired air. The samples of air were analysed in the Haldane apparatus. Two blood samples from the ear were taken every 15 minutes, the blood sugar concentration being determined by the method of Hagedorn and Nor-
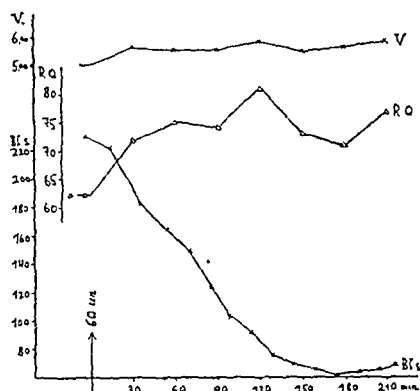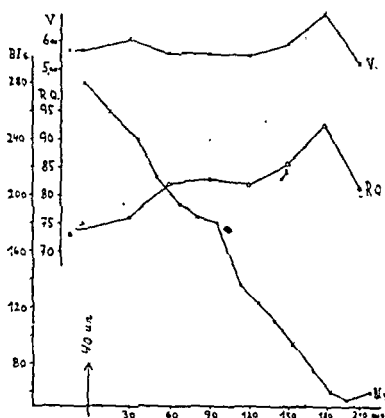
Fig. 2.   Fig. 3.

man Jensen. The blood pressure was followed every 10—20 minutes as an indicator of adreno-sympathetic counterregulation.

The changes of ventilation in this kind of experiments can be regarded as a control of the »reality» of the RQ.

Experiments.

1) Case 2181/43, a woman aged 25 years. .Diabetes recently diagnosed. Treated for two weeks with »Free diet ÷ Sugar» (a normal diet, omitting only extra sweetening of the meals at table, sugar in the tea, »sweets», chocolate, etc.). 24 units of insulin + 48 units of Protamine Zinc Insulin (PZI). Glycosuria: 1—4 g per day. No ketonuria. 24-hour blood sugar series 2 days before the experiment gave values ranging between 96 and 270 mg %.

No insulin the day before the experiment.

Fig. 2 After 60 units of insulin great fall of blood sugar. The RQ is low, 0.62, before the injection. After the injection a considerable increase is seen, to 0.81. RQ begins to fall when the fall of the blood sugar ceases. In the last period a secondary rise of RQ. (This is due possibly to the slight rise of the blood sugar noted at this junction, possibly to a discharge of adrenalin, as such a rise has been met with occasionally also in normals *without* increase of the blood sugar. (Lundbæk, 1943).

Ventilation: slight rise. — Total metabolism. Before injection 106 %. Fall in the second half of the experiment to 100 %. — Symptoms: from 145' minute to the end of the experiment sweating attacks with rise of blood pressure.

2) Case 1822/43, a man aged 20 years. Insulin treated diabetes of 3 years duration. Diet: Bread 200 g, potatoes 150 g, for the rest »Free diet ÷
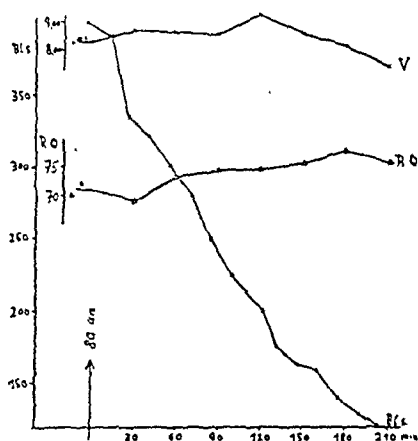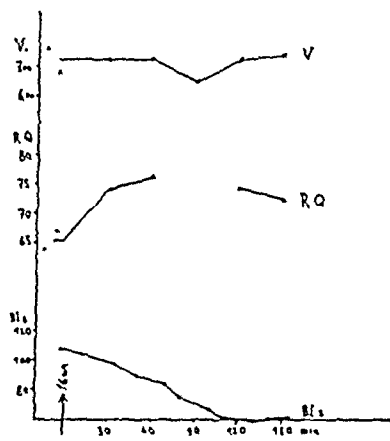
Fig. 4.

Fig. 5.

Sugar». 20 units of insulin + 54 units of PZI. Glycosuria: 5—20 g per day. No ketonuria. 24-hour blood sugar series gave values between 106 and 370 mg %.

No Insulin the day before the experiment.

Fig. 3: Great fall of blood sugar after 40 units of insulin. The RQ rises considerably, from 0.74 to 0.93. A little plateau is seen on the midst of the RQ curve. At the same time there is a clearcut decrease in the steepness of the blood sugar curve. The last period shows fall of the RQ, simultaneously with cessation of the blood sugar fall.

Ventilation: rise in the 8' period. — Total metabolism: initial value 110 %. Fall to 105 %, rise again in the last period to 115 %. — Symptoms: from 200' minute sweating and rise of blood pressure.

3) Case 99/44, a man aged 25 years. Insulin treated diabetes since 1937. Diet: »Free diet ÷ Sugar». 36 units of insulin + 36 units of PZI. Glycosuria: 50—200 g per day. No ketonuria. 24-hour blood sugar series 6 days before the experiment: 89—250 mg %.

Fig. 4: After 80 units of insulin a very great and steep fall of the blood sugar. The RQ curve rises slowly from 0.71 to 0.77. In the last period little fall of the RQ. The blood sugar curve shows only insignificantly decreasing steepness in the latter half of the experiment.

Ventilation: Maximum 2 hours after the injection, followed by fall. Total metabolism: initial value 131 %. In the last 3 periods fall to 125— 118—125 %.

Symptoms: no hypoglycemic symptoms.

4) Case 1245/43, a man aged 18 years. Insulin treated diabetes since 1940. Diet: »Free diet ÷ Sugar». 8 units of insulin + 36 units of PZI. Gly-
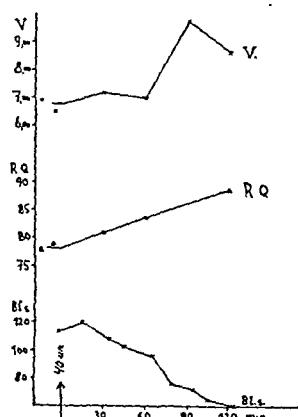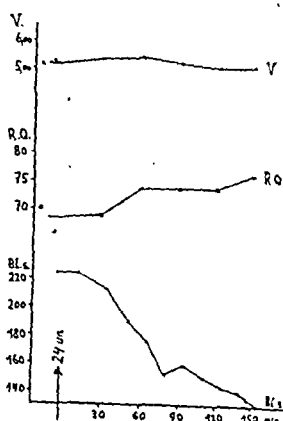
Fig. 6.

Fig. 7.

cosuria: 0—2 g per day. No ketonuria. 24-hour blood sugar series gave values between 50 and 170 mg %.

Fig. 5: After 16 units of insulin a little fall of the blood sugar to a new lower level at about 60 mg %. RQ rises from 0.65 to 0.76, then falls. The course of the RQ curve at the top is uncertain, owing to the loss of the 5' period, but the RQ values are seen to fall during the new blood sugar equilibrium.

Ventilation: Fall in 5' period. — Total metabolism: initial value 99 %, fall to 91 % in 6' period, followed by a new rise to 101 %.

Symptoms: no hypoglycemic symptoms.

5) Case 1832/43, a man aged 35 years. Diabetes recently diagnosed. Diet: »Free diet ÷ Sugar». 40—50 units of PZI, the last 2 days supplemented with 24 units of regular insulin. Glycosuria: 130—180 g per day. No ketonuria. 24-hour blood sugar series the day before the experiment: 260—410 mg %.

Fig. 6: After 40 units of insulin slow and somewhat uneven fall of the blood sugar. RQ rises in a straight line from 0.785 to 0.89.

Ventilation: Very great rise in 5' period, probably hyperventilation. The corresponding sample of air has been lost.

Total metabolism: initial value 113 %, fall to 98 % in the last period.

Symptoms: Sweating and rise of blood pressure from the 90' minute.

6) Case 1730/43, a woman aged 50 years. Diabetes diagnosed just before admission, 4 days before the experiment. Diet: »Free diet ÷ Sugar». 16 units of PZI. Glycosuria: 10—50 g. No ketonuria. 24-hour blood sugar series the day after admission gave values ranging between 210 and 310 mg %.

No insulin the day before the experiment.

Fig. 7: Great fall of blood sugar after 24 units of insulin. The fall is steep in the beginning, but there is an uneven plateau from the 80' to
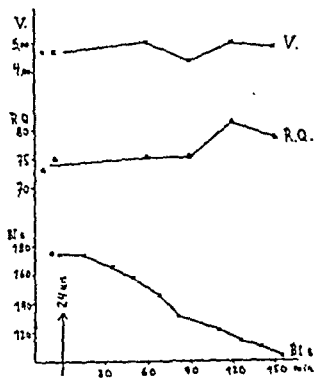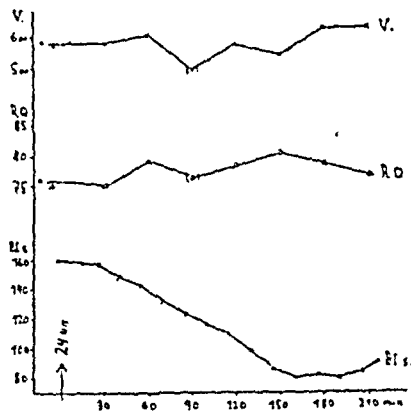
Fig. 8.

Fig. 9.

the 110' minute, followed by a new fall. The RQ curve rises from 0.68 to 0.74, persists at this value from the 60' to the 120' minute, and then rises further.

Ventilation: practically unchanged. — Total metabolism: initial value 105 %, fall to 94 % during the experiment. — Symptoms: no hypoglycemic symptoms noted.

7) The same patient as in nr. 6.

The experiment took place 8 days after the former one. Diet unchanged, 24 units of PZI. No glycosuria, no ketonuria. 24-hour blood sugar series 2 days before the experiment: 110—225 mg %.

Fig. 8; A moderate fall of the blood sugar after 24 units of insulin. The fall is a little steeper in the first half of the experiment than in the second. No rise of the RQ for the first 90 minutes, then a rise and a fall, without any corresponding changes in the steepness of the blood sugar fall.

Ventilation: only minute changes. — Total metabolism: initial value 88 %; practically no changes during the experiment. — Symptoms: no hypoglycemic symptoms.

8) Case 999/44, a man aged 47 years. Diabetes recognized shortly before admission. Diet »Free diet ÷ Sugar». Without insulin a glycosuria of 4—6 g per day is found, no ketonuria. 24-hour blood sugar series shows values from 160 to 230 mg %. The day before the experiment insulin is given for the first time, 16 units of ZPI.

Fig. 9; After 24 units of insulin a moderate fall of the blood sugar is seen. At about 80 mg % a new plateau is formed. The RQ curve rises from 0.755 to 0.80 in the 7' period. After this there is a fall, corresponding to the blood sugar plateau. The decrease of RQ in the 5' period is probably not »real», as is seen from the abrupt decrease in ventilation. The patient was on the verge of falling a sleep in this period. Such variations of ventilation and RQ are characteristic of the onset of sleep (Magnussen, 1944.)

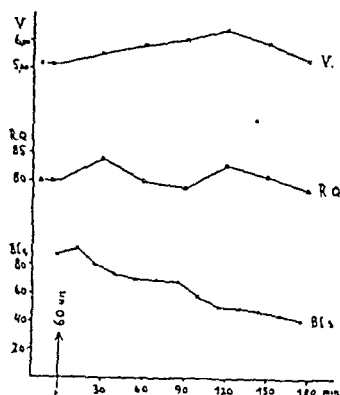Ventilation: se above. — Total metabolism: insignificant changes

Fig. 10.

during the experiment, except at the 5' period, where a fall is seen (onset of sleep).

Symptoms: from 180' minute rise of blood pressure. No other hypoglycemic symptoms.

9) Case 679/44, a woman aged 30 ·years. — Insulin treated diabetes for one year. Diet: »Free Diet ÷ Sugar». 20 units of insulin + 40 units of PZI. — Glycosuria: 20—40 g per day. No ketonuria.

Fig. 10: After 60 units of insulin a little fall of the blood sugar is seen, followed by a plateau at about 70 mg %. Then a new fall and a new plateau at about 45 mg %. On the RQ curve two peaks are noted, corresponding to the decreases of blood sugar.

Ventilation: increasing to a maximum in the 6' period. Total metabolism: initial value 95 %. Rise to 115 in the 6' period, then fall to 107 %. — Symptoms: 90 minutes after injection sweating and rise of blood sugar. After the last period hypoglycemic precoma.

Discussion.

It appears from these experiments, that the correlation generally found in normal individuals after injection of insulin between the RQ curve and the blood sugar curve, can be demonstrated also in most cases of diabetes.

The interpretation of this correlation is, however, much more difficult when dealing with the diabetic than with the normal organism. Although none of the patients examined showed ketonuria by the usual tests for acetone and diacetic acid, it is to be supposed that in all, or at least in some of the cases, there was an abnormally increased rate of gluconeogenesis.

It is not sure, therefore, that the RQ values obtained are true RQ's of catabolism. The common finding of RQ values below 0.70 is a proof that in some cases they are certainly not.

On account of such abnormalities in the metabolism of diabetics, evidently the rise of RQ in these experiments may have been caused by a decrease in gluconeogenesis just as well as by an increase of carbohydrate combustion. On the other hand the fall of RQ may have been called forth by increasing gluconeogenesis as well as by decreasing carbohydrate combustion.

No doubt in some cases (and perhaps always) variations of gluconeogenesis with relation to the form of the blood sugar fall are taking place after administration of insulin to diabetics. This has been demonstrated by Jacob Poulsen in his investigations on the blood ketones (1941), which show exactly the same correlation between the ketone curve and the blood sugar curve as has been shown in this paper between the RQ curve and the blood sugar curve. In most of his cases the blood ketones are falling during the blood sugar fall, rising again when the blood sugar fall is over.

Taking into account, however, the carbohydrate combustion actually occuring in the diabetic organism (Soskin & Levine, 1937), it seems most probable, that the rise and fall of the RQ in diabetics is caused by variations of carbohydrate combustion as well as of gluconeogenesis, both processes being related to the variations of the blood sugar concentration.

Summary.

The same correlation which was demonstrated previously in normal subjects between the course of the RQ curve and the form of the blood sugar curve has been found in most cases of diabetes.

The cause of this correlation is thought to be variations of the carbohydrate combustion as well as of gluconeogenesis.

These processes both seem to be related to the *variations* of the blood sugar, not to its actual *level*.

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Uremia in morphine addicts.

By

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(Submitted for publication August 21, 1944).

It is a well known fact that morphine addicts gradually become increasingly cachectic. In some cases suicide brings an end to the patient's life, in other cases death is due to an intercurrent infection. Some patients however die in a cachectic state without any manifest infection; in such cases the cause of death will presumably be given as morphine cachexia.

However no satisfactory and sufficient explanation of the cachexia has been given. In this paper 4 cases of chronic uremia in morphine addicts are reported. 2 of the patients, both of them cachectic, died from uremia, and post mortem examinations showing severe renal damage have been undertaken. The other 2 patients were also more or less cachectic.

The author feels that impairment of the kidney function may in some cases contribute in an important way to the development of the cachexia of morphine addicts. Even in severe uremia no albuminuria may be found and the uremia is only disclosed by chemical examination of the blood. Hence these patients may very well die without the right diagnosis having been made.

Case histories.

Case Number I.

1104/43, woman, 67 years old. Symptoms of gastric ulcer since 1932. Congenital subluxation of right hip-joint, since 1932 much pain from deforming arthrosis here. Several stays in hospitals for these diseases. Since

1932 daily use of morphine in moderate doses. During stay in hospital for 6 weeks, Oct.-Nov. 1942 for depression, no albuminuria (6 examinations), readmitted in December 1942, transferred to mental hospital Jan. 1943. During this stay for some days frequent micturition, the urine contained trace of albumin, but catheter specimen was normal and culture were negative. Morphine was discontinued during the stays in hospitals, but after discharge the patient very soon resumed her use of this drug. On readmission July 23. 1943 she had hallucinations, was emaciated, pale and restless. On admission the urine contained no albumin. Catheter specimen was normal and culture was negative. Severe azotemia and acidosis was found (see below). Muscular twitchings were present. A tumor as large as a Jaffa orange could be felt over the symphysis (later proved to be a benign ovarial cyst).

She was given intravenous bicarbonate, fluids and diet and improved considerably. She became quiet and the muscular twitchings gradually subsided. For 10 days falling doses of morphine were given till finally discontinued. She was discharged on Oct. 14th much improved and mentally normal. On Now. 1st she was admitted to the surgical dept. and operated on for the ovarial cyst. She died here on Nov. 14th 1943.

Laboratory findings etc.

Urine on admission July 1943: 0 alb., later trace of alb.

Catheter specimens: no casts, a few leucocytes, July 24th culture negative, July 30th *coli*, Aug. 10th culture negative.

Blood-urea: July 26th: 260, 27th: 250, Aug. 3.: 192, slowly decreasing, Oct. 15th: 134 mg %.

Alkalireserve: July 26th: 22 vol. %, 27th: 37 vol. %, July 31st: 69 vol. %.

Standard-clearance of urea: July 30th: 4 ml. per min.

Addis' concentration test: July 31st: Maximum conc.: 1005.

Total protein in Serum: 7.3—5.7 %.

Urography: Aug. 14th: no excretion of perabrodil in pelves or bladder. The kidneys cannot be seen.

Oftalmoscopy: no retinal changes.

Blood pressure: 180/120, 200/110.

Hemoglobin sicca: 50 %, did not rise.

Sedimentation rate: 93—100 mm in 1 hour.

Post mortem examination showed the heart moderately enlarged.

The kidneys and urinary tract: no hydronephrosis. Kidneys contracted, right 9 × 4 × 2 cm., left 9 × 4.5 × 2.5 cm. Capsule adherent, but strips easily. The surface is greyish-yellow with somewhat irregular granulation. The cortex is very narrow. On section the surface is greyish-yellow with disseminated minute cysts (2—3 mm).

Height 161 cm. *Weight:* 47 kg.

Summary: Woman, 67 years old. Used opiates for about 11 years originally for pains from arthrosis of the hip-joint and gastric

ulcer. During a stay in hospital in Dec. 1942 she had for a short time moderate dysuric symptoms. The urine contained trace of albumin, but catheter specimen was normal. July 1943 she was admitted with severe uremia. Renal function test showed severe impairment of function. Coli bacilli were found in the urine; albuminuria only present now and then. She died in November 1943 and post mortem examination showed contracted kidney probably of pyelonephritic type.

Case Number II.

317/44, woman, 46 years old. Hemicrania since she was 19 years old. Since 1932 she had used tablets with acetanilide. In 1934 in hospital for anemia toxica. The headache persisted; since 1937 she used pantopon daily, often scopolamine. In 1938 she was in hospital and the use of pantopon (+ scopolamine) was stopped, but after discharge she very soon resumed her habit; during several stays in hospital she improved, but these was no lasting effect. *In Dec. 1940* she had for the first time *frequent and scanty micturitions*, but the urine was normal. X-ray examination after perabrodil at this time (Jan. 6th 1941) showed the kindeys of normal size, but the excretion was not good, however the pelves could just be discerned. On *Jan. 5th 1943* she was admitted in a very serious condition, she was uremic (see below). The urine contained trace of albumin the next day. By treatment with fluids, bicarbonate and diet she improved, but was still emaciated and anemic on discharge March 12th 1943. On account of uremia she had to go to hospital several times till she at last died on February 14th 1944. She had used opiates at home and had steadily deteriorated except for slight improvements during her stays in hospital. Albuminuria was only found intermittently, and when present only slight traces were found.

Laboratory findings etc.:

Urine see above.

Catheter-specimens never showed abnormal cells, no casts.

Cultures negative.

Blood urea: Jan. 6th 1943: 142, slowly decreasing, March 1943: 114, Sept. 20th 1943: 98, Nov. 22th 1943: 88, Febr. 2nd 1944: 238 mg %.

Alkalireserve Jan. 7th 1943: 11, after a few days normal, Febr. 12. 1944: 21 vol. %.

Maximum-clearance: Febr. 12th, 1943: 13, June 2nd 1943: 11 ml. per minute.

Addis concentration test: Febr. 28th 1943: Maximum conc. 1013.

Total-protein: Jan. 7th 1943: 7.1 %.

Urography (see also above): Febr. 17th 1943: no excretion.

Ophtalmoscopy: no retinal changes.

Blood pressure always normal.

Hemoglobin (sicca): 55 %, normochromic anemia, *some improvement* by treatment, but rapid relapse.

Weight: July 1938: 55 kg., Sept. 1943: 50 kg.

X-ray examination of cranium: moderate frontal hyperostosis..

Post mortem findings: Pyelonephritis chronica, Hydronephrosis duplex. Hyperostosis frontalis. Anemia. Cholelithiasis.

Both kidneys were small (right: 9 × 4 × 2.5 cm., left: 8 × 4.5 × 2.5 cm.) Capsule adherent. Surface very irregular with many small cysts and scars. On section several minute cysts, calyces dilated. Pelves and ureters dilated. Ureter measures 6 mm.

Microscopy: Pelvis thickened. Parenchyma very narrow. Considerable proliferation of the interstitial fibrous tissue, somewhat patchy, in the fibrous tissue considerable mononuclear infiltration. Glomeruli to a large extent fibrous or hyaline. In the fibrous tissue rests of small atrophic tubuli. Between the fibrous parts smaller parts with somewhat better parenchyma, here tubuli are dilated; here and there some glomeruli with less changes are seen. Arteries and arterioles are very sclerotic.

Summary: woman, 46 years old, who on account of hemicrania had used first tablets with acetanilide, anemia had developed, later (since autumn 1938) she began to use opiates (pantopon and codeine). Slight and transient dysuric symptoms appeared in Dec. 1941. Kidney function was found impaired in Jan. 1942, uremia developed January 1943. Albuminuria was inconstant and slight. She died from uremia in Febr. 1944. A pyelonephritic contracted kidney was found.

Case Number III.

Woman, 43 years old. 26/44.

Hemicrania since 1926, since 1932 tablets with 1 ctg. morphine and 1 ctg. codeine were taken 3—4 times a day. Tuberculous irritis from 1932, in hospital in 1934 and 1937, no albuminuria. 1941 her left eye was removed. June 1943 in neurosurgical dept., no albuminuria, transferred to medical dept. July 29th 1943. She was pale, emaciated, very weak. *For 2 or 3 years moderate dysuric symptoms.* Urine contained albumin, catheter specimens showed many leucocytes, culture: coli bacilli. Considerable azotemia, moderate acidosis was found; severe anemia. Treatment with fluids, bicarbonate and later sulphathiazol caused slow but steady improvement. Opiates were gradually reduced, but she could not do without a little dilaudid (0.8 mg per day).

Laboratory findings etc.

Urine: The pyuria was improved, but the urine did not become sterile. The albuminuria was at the beginning about 0.5 °/oo, presently 0.

Catheter spec.: see above.

Blood urea: July 30th: 170, Aug. 3rd: 240, Aug. 9th: 264, then rapidly decreasing, Aug. 19th: 118, Sept. 3rd: 80, Febr. 12th: 36 mg %.

Alkalireserve: July 30: 40, Aug. 14: 58. vol. %.

Maximum clearance: January 16th: 30 ml per minute, Febr. 12th; 17 ml per minute.

Addis concentration test: January 22nd: 1010.

Urography: Febr. 4th: delayed excretion, not till after 45 minutes visible contrast in pelves. Kidneys seem to be rather small.

Ophtalmoscopy: no retinal changes.

Blood pressure: always normal.

Hemoglobin (sicca) July 30th: 50 %, normochromic anemia, Febr. 8th: 80 %.

Weight: Jan. 1935: 50 kg., July 1943: 38 kg., Febr. 1944: 40 kg.

Summary: woman , 43 years old, with hemicrania and tuberculous iritis, who for 12 years had used morphine and codeine in moderate doses. For 2 years moderate dysuric symptoms, on admission pyuria (Coli) and uremia good improvement on treatment, on discharge she had normal blood urea, but the kidney function was bad.

The sister of this patient had also hemicrania and had for many years used morphine injections — during the last time 6 ctg. daily. She died in another hospital with a phlegmone femoris and *uremia* (blood urea 220 mg %).

Case Number IV.

Woman, 63 years old., 1503/43.

Since 1928 trigeminus neuralgia, used large doses of »mixed powders« with acetanilide. Anemia found in 1928, resistent to treatment. 1935 *operated on for neuralgia of the left Vth nerve without much effect.*

Since 1936 she used gtt. thebaica comp. 30 drops 3 times a day = 6 ctg. opium per day; in bad periods she also had morphine injections. Several febrile attacks of pyuria, first in 1938.

In hospital Oct. 15th—Nov. 15th 1943 for weakness and trigeminal neuralgia. She was pale, but not severely emaciated. The urine contained no albumin. Blood-urea was found elevated (see below).

She improved slightly on treatment with rest, Fe and B vitamin.

Laboratory findings etc.

Urine: see above.

Catheter specimens: many leucocytes. Culture: bac. coli.

Blood-urea: Oct. 26th: 68, 28th: 72, Nov. 9th: 78 mg %.

Maximum-clearance: 17 ml per minute.

Addis concentration test: 1011.

Urography: no excretion, even after 8 hours. The right kidney measures 10.5 × .5 cm., the left cannot be seen.

Total-protein in serum: 6.3 %.

Oftalmoscopy: no retinal changes.

Blood-pressure: 155/80, 160/90.

Hemoglobin: (sicca): 65 %, normochrome anemia, no certain improvement.

Ewalds test meal: Achylia.

Height: 163 cm.

Weight: 55.7—54.7 kg.

Summary: 63 years old woman with trigeminal neuralgia for 15 years. For 7 years she had used opiates regularly. Several attacks of pyuria since 1938. In Oct. 1943 when no albuminuria was present her kidney function was found impaired (maximum-clearance 17 ml per minute, Addis test 1011), blood-urea about 70 mg %. pyuria (Coli) was present.

These patients have some clinical features in common. They are all women who for many years have used opiates for painful chronic diseases; the amount used is in all cases rather moderate. They have all had dysuric symptoms; these have occurred several years after the use of opiates had begun; the symptoms have never been very pronounced, in 3 of the cases only consisting of frequent micturitions; only one of the patients had several years before azotemia was diagnosed had febrile attacks of pyuria, and she had, when azotemia was found, no dysuric symptoms whatever. Only slight and inconstant albuminuria was found, even if severe uremia was present. In 3 cases leucocytes and coli bacilli were found in catheter specimens of the urine, but the pyuria was not massive and cultures were not constantly positive. Post mortem examination in the fourth patient showed characteristic pyelonephritic contracted kidney. So subjective symptoms from the urinary system were only slight and could easily be overlooked. As albuminuria was slight and transient, the headache, nausea, vomiting, weakness and emaciation might easily have been ascribed to »morphine cachexia» combined with the other diseases from which the patients were suffering.» Function tests showed severe renal impairment in all cases. Retinal changes were not found. Only 1 patient (67 years old) had definite elevation of the blood pressure. The doses of morphine used by these patients have as

mentioned not been exceedingly large. One patient (case No III) used about 4 ctg morphine + 4 ctg. codeine per day for about 11 years; it is probable that her informations on this point were reliable. Another patient (case No II) used certainly more, how much cannot be exactly stated; for the most time it seems to have been 4 ctg. morphine + 8—12 ctg. codeine phosphate daily; the use of opiates went on for about 6 years. One patient (No IV) used 6 ctg opium daily + injections of morphine in her bad periods. She used opiates for 7 years. In case No I the exact amount cannot be stated but seems to have been rather large, even if not exceedingly large, and the abuse went on for 12 years.

The pathological findings in the 2 patients who died were very much alike. It was the characteristic picture of the pyelonephritic contracted kidney. It is reasonable to believe that the 2 other patients also have pyelonephritis with some degree of contraction.

Now one must ask whether the combination of chronic use of opiates and pyelonephritis with severe impairment of kidney function owing to chronic pyelonephritis is merely a coincidence or if a causal connection is present. Or to put the question in another manner: in which way may the prolonged use of opiates cause pyelonephritis? It is a well known fact that morphine may cause disturbance of micturition; the emptying of the bladder is difficult and incomplete partly because of the decreased desire to micturate, partly because of the effect of morphine on the autonomic innervation of the bladder. This incomplete emptying of the bladder naturally disposes to infection of the urine, especially in women. Furthermore morphine has an effect on the ureter and renal pelvis which has been studied by Ockerblad (J. urology, *33*, page 356, 1935). It has been shown that morphine causes a rise of the ureteral pressure. This rise may conceivably cause some degree of stagnation of the urine in the pelvis, and this naturally again creates great possibilities for an infection to ascend into the renal parenchyma.

So it seems quite reasonable to believe that the prolonged use of morphine may be the indirect cause of chronic pyelonephritis which ultimately may lead to pyelonephritic contracted kidney.

It is significant that all 4 patients were women who are much more liable to contract infection of the urinary tract than men.

I have not been able to find any cases of uremia in morphine

addicts in the litterature. This is probably due to the fact previously pointed out that urological symptoms are rather vague and the uremic symptoms are more or less obscured by the symptoms of chronic morphinismus. Furthermore patients with chronic morphinismus are mostly treated in mental hospitals where attention is generally not directed towards kidney function and the urinary tract.

As the effect of morphine in these patients is not a toxic effect on the kidneys but a complication produced by the disposition to ascending infections caused by the effects of the drug on the urinary tract, it is obvious that not all morphine addicts will show this complication. Men must be by far less exposed to it, and of course only a certain number of women will have their urinary tract infected. Ceteris paribus the longer the abuse has taken place the greater the proportion of patients with pyelonephritis. I have during recent years treated 8 morphine addicts in all, including the 4 patients referred to in this paper. The other 4 had no signs of ·pyelonephritis or renal damage.

They had been using opiates for

1) 4 months, normal urine, normal kidney function
2) 10 . »   »   »   »   »   »
3) 2 years and
    3 months   »   »   »   ·   »   »

4) 8 years this latter patient had for the last 2 years not used opiates but dolantin which is somewhat like atropine in its effects on the autonomic nerves. Ockerblad has shown that atropine abolishes the effect of morphine on the ureteral pressure and no effect on the bladder is known. Hence 3 of these patients have been using opiates for a considerably shorter time than those described with renal damage. The fourth patient has never had dysuria, on examination in May 1944 she had normal urine and normal kidney function.

The material presented is small. But in view of the facts concerning the effects of opiates on the bladder and the importants observations of Ockerblad, I believe that it is sufficient to show a relationship between the prolonged use of opiates and renal damage owing to chronic pyelonephritis.

It would be interesting to have this suggestion confirmed by investigations on a large material of morphine addicts.

Summary.

4 cases of severe renal impairment owing to chronic pyelonephri- tis in women who had used opiates for a long time are reported. The dysuric symptoms have been very vague, signs of renal disease (albuminuria et c.) slight and transient so that the renal insuffi- ciency might easily have been overlooked.

The author suggests that chronic uremia may in some cases contribute to the cachexia in morphine addicts.

Functional disturbances of the atrio-ventricular conduction.[1]

By

OTTO JERVELL.

(Submitted for publication August 8, 1944).

Introduction.

The electrocardiographic examination has learned us that disturbances of atrio-ventricular conduction are seen frequently, and are not seldom the only electrocardiographic finding and the only sign of a heart disease. The aim of the present investigation was to find out how often functional disturbances of the A. V. conduction occur, and which importance one might attribute to a prolonged PQ interval in the electrocardiogram.

There has been some lack of aggreement as to the normal PQ interval. As the upper limit of the normal values one has previously been used to regard 0.18 sec. Newer investigations have however shown this limit to be too narrow.

Korth in his text-book (p. 239) says that the upper limit of the normal PQ interval usually is fixed at 0.18 sec, and he adds that values higher than 0.20 sec. at any rate have to be regarded as pathological. Uhlenbruch (p. 351) sets also the upper limit at 0.20 sec. Larsen and Skulason regard the values as pathological if the PQ interval in at least one lead be 0.22 sec. or more. The PQ interval is in some degree dependent of the heart rate. If there is more pronounced tachycardia figures of 0.17 or 0.18 sec. will arouse suspicion as to a disturbance of A. V. conduction (Korth, p. 239).

[1] Concluded May 15, 1943.

An increase of the PQ interval during the course of a disease is like-wise of importance. If in the course of a rheumatic fever an in-crease of the PQ interval from e. g. 0.16 to 0.20 sec. is observed this would probably be a sign of the A. V. bundle being damaged. In the present material only cases are included, where at least once a PQ interval of 0.22 sec. or more was observed in at least one lead.

The atrio-ventricular bundle is rather sensitive to injury. It is not easy though to decide whether the disturbance of A. V. conduction observed be due to an organic disease, or be functional in nature. As functional disturbances many authors, e.g. Pardee (p. 66), only consider alterations of quite transient character, which are only detectable so long as the active substance in ques-tion displays its action. This definition however cannot be main-tained. We find on one side permanent changes of PQ in indivi-duals without organic heart disease, for instance as a residue after a rheumatic fever or diphtheria. Organic changes, on the other hand, may be transitory.

Several authors, such as Volhard, Hecht, and others, have claimed that atropine could be used to separate the functional from the organic disturbances of A. V. conduction. Wenckebach and Winterberg (p. 298) however rightly point out that this implies that the functional disturbances of A. V. conduction are brought about by increased vagus tone. If after atropine complete or par-tial retrogression of the disturbance of conduction is observed, this would only show that there is a functional factor involved, but one would not be allowed to conclude that there did not exist any organic disease. A more correct valuation of the nature of the disturbance of conduction is therefore obtained by studying the whole clinical picture, say Wenckebach and Winterberg (p. 299).

The Material.

During the last years the author has treated 317 patients with disturbances of A. V. conduction, 38 of whom were his private pati-ents. In all of the hospital patients a Wassermann's and/or a Mei-nicke II reaction were carried out. In my private patients these tests were only made in cases where a luetic infection was sus-pected. In the greater majority of the patients a series of electro-cardiograms was taken.

Table 1.

317 Cases of Disturbances of Atrio-Ventricular Conduction. Age and Sex.

Age Group	10—19	20—29	30—39	40—49	50—59	60—69	over 70	Total
Men	3	8	15	23	29	53	30	161
Women	1	15	17	22	34	31	36	156
Both Sexes....	4	23	32	45	63	84	66	317

As shown in table 1 the material is composed of an equal number of men and women. If the material be divided in two groups, individuals below and above 50, there will not be to be found any difference in between the number of the men and that of the women.

All the cases arranged according to their etiology, are contained in table 2.

Table 2.

317 Cases of Disturbances of Atrio-Ventricular Conduction. Etiology.

Diagnosis	Number of Cases
Degenerative Heart Disease	146
Rheumatic » »	43
Luetic » »	14
Congenital » »	1
Graves' Disease. Hypothyroidism	11
Acute Infections	15
Gastric and Duodenal Ulcers	36
Observatio cordis. Neurosis cordis	39
Anæmia	12
In all	317

Of the 317 patients examined 10 had a complete A. V. block, 12 had a second degree or partial block, while the remaining 295 had a prolonged atrio-ventricular conduction time without lack of the ventricular systole.

Degenerative Heart Diseases.

In many cases it will be difficult to decide whether a chronic heart disease is due to sclerotic changes or to high blood pressure. One will namely in many cases of hypertension not seldom find anatomical changes in the vessels, arteriosclerosis. The hypertonic and the sclerotic cases are therefore gathered in one group labelled degenerative heart diseases. This group also includes two cases of aortic stenosis and three cases of aortic regurgitation with unknown etiology. All these patients, except 6, were over 50. In all we find in this group 146 cases, 4 of which had a complete block, 7 had a partial block, while the remaining 135 had a first degree block, 9 patients had infarctions of the heart (6 infarctions of the anterior wall and 3 of the posterior).

Of other electrocardiographic findings may be mentioned that 6 patients had a sinoauricular block, and 24 branch block (17 of the most common type, 2 rarer types, and 5 Wilson's block). Only 15 patients had, apart from the prolonged A. V. conduction, a normal electrocardiogram.

The longest PQ interval recorded (0.53 sec.) without lack of ventricular systole was found in a man aged 66 with arthritis urica and hypertension. At the same time there was sinus-bradycardia. (Possibly there may have been a 2:1 sino-auricular block.)

In 10 cases *digitalis* had been a concurrent cause in the production of the block (first degree block). In 5 cases one had to deal with paroxysmal tachycardia (fibrillations) treated with digitalis, where the PQ interval was found lengthened after the action of the heart had become regular.

It is of no interest to discuss the cases in detail. One must take it for granted that all the patients belonging to this group suffered from organic heart diseases. If one in patients with degenerative heart diseases finds disturbances of A. V. conduction, one will as a rule assume that there are anatomical changes causing the block. The anatomical substrate may be myomalacic foci, hemorrhages or cicatricial tissue in the bundle of His. In certain cases sclerotic changes in the vessels will lead to impaired circulation in the bundle of His, and cause a reduction of its conductive power.

There exists however the possibility that it is an *enlargement of the heart*, that has brought about an impairment of the conductive power of the bundle of His, what has been emphasized by the author in a previous paper (Jervell and Laake). Chronic coronary insufficiency will be able to affect the blood supply to the specific muscle fibres of the heart (Büchner). Dilation of the heart might also be thought to stretch the bundle of His, thus causing an impairment of conductive power.

In the present material 87 of the 146 patients were examined roentgenologically. In 53 of the 87 patients (61 % per cent.) an enlarged heart was found. The electrocardiographic findings in these 53 patients were highly varying, depletion of the ST-line in one or several leads, negative or flattened T-waves, left preponderance, bundle branch block etc. being observed.

It may be difficult in every case to decide whether a prolongation of the PQ interval is due to sclerotic changes or to an enlarged heart. This applies, besides, also to other electrocardiographic findings. Rasmussen and Thingstad have thus shown that a branch block electrocardiogram may be encountered in hypertension with cardiac hypertrophy, as a consequence of a retarded propagation of the irritament by the considerably hypertrofic muscle fibres (Fahr, Weber, and others). If one, therefore, in a patient with hypertension and an enlarged heart finds a branch bundle block and a lengthening of the PQ interval, I mean that both these electrocardiographic changes are due to the enlargement of the heart and not to sclerotic processes.

If one assumes that hypertrophy and/or dilation of the heart may cause disorders of conduction in the bundle of His, the question arises whether a complete block also might develop in the same way. This is possibly less likely, but an enlargement of the heart may anyhow be thought to be a concurrent cause in the formation of the block. In one of our patients, a man of 80 with aortic regurgitation of unknown etiology, I found thus a considerably enlarged heart, complete A. V. block, branch bundle block and auricular fibrillations.

The objection may be raised against this theory of an enlargement of the heart being the cause of disturbances of A. V. conduction, that a prolongation of PQ is relatively seldom found in hypertrophy and dilation of the heart. It must, however, be remem-

bered that in the later stages of cardiac dilation, e.g. in mitral stenosis, one gets auricular fibrillation, which makes it impossible to observe variations of the conductive power. It is likely though that the bradycardia that may be seen in many cases of fibrillations, which were not treated with digitalis, is due to an increasing partial block. These cases are also sensitive to digitalis, even relatively small doses causing a total block.

Table 3.

Length of PQ Interval before and after 1 mg Atropine in 10 Patients with Organic Heart Disease.

No.	Sex.	Age.	Disease.	PQ Interval	
				Before 1 mg Atropine	After 1 mg Atropine
1	♀,	48 years	Angina pectoris. Cholelithiasis......	0.22 sec	0.19 sec
2	♀,	64 »	» » »	0.25 »	0.22 »
3	♀,	55 »	» » Bundle Branch Block.	0.22 »	0.17 »
4	♀,	55 »	Coronary Sclerosis. Bundle Branch Block	0.22 »	0.22 »
5	♀,	72 »	» »	0.25 »	0.24 »
6	♂,	67 »	» »	0.22 »	0.19 »
7	♀,	39 »	Nephritis chronica. Lues Latens ..	0.27 »	0.17 »
8	♀,	42 »	Mitral Stenosis + Aortic Regurgitat.	0.24 »	0.22 »
9	♂,	50 »	» » + » »	0.22 »	0.22 »
10	♂,	23 »	Vitium cordis congenitum	0.22 »	0.21 »

In two cases I observed a *shortening* of the PQ interval during digitalis therapy. In one case PQ was reduced from 0.25 to 0.21 sec. after in all 1.6 g digitalis. This was the case of a man aged 68 with hypertonia and enlargement of the heart (Goedel's index 1.7). These cases might possibly be taken as a support of the theory of the enlargement of the heart as a cause of inhibition of conduction in the bundle of His.

In a number of cases in this group I found PQ intervals changing from day to day. This points to the existance of a concurrent *functional* factor. If an anatomical substrate was the only cause of the impaired conduction, one ought to find a constant PQ interval. In many cases the PQ interval was reduced after atropine (table·3). I will come back to these experiments later.

Rheumatic Heart Diseases.

Of rheumatic heart diseases with disturbances of A. V. conduction in all 43 cases were observed, viz. 12 patients suffering from rheumatismus acutus respectively polyarthritis rheumatica subacuta, 2 cases of pericarditis, 2 of endocarditis and 28 of valvular diseases.

Among the 15 cases in the acute respectively subacute stage the PQ interval was from 0.22 to 0.27 sec. In one case there was a second degree block.
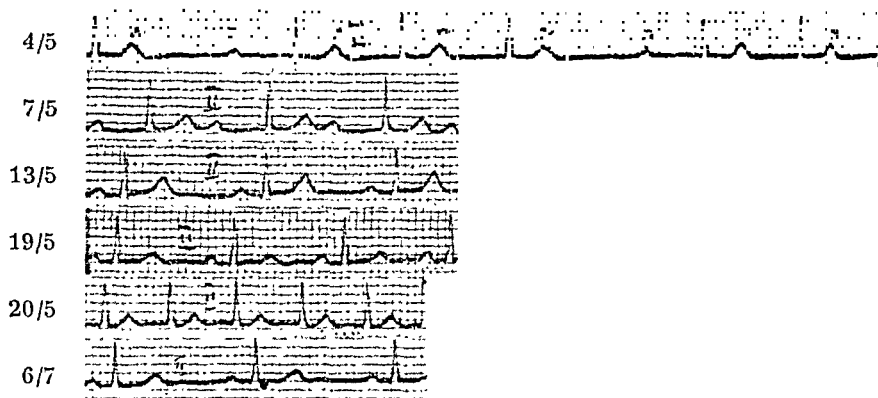

Fig. 1. E. O. H. ♀, aged 28. *Rheumatismus acutus.* Tonsillitis chronica. Electrocardiograms: May 4. Partial block — Type 2; May 7. PQ 0.37 sec.; May 13. PQ 0.17 sec. after atropine (case 1).

It is a clinical experience that a first degree block frequently develops in rheumatic infections, while partial and complete blocks are relatively seldom. Lepeschkin states that one in acute rheumatism may find values for the PQ interval up to 0.50 and 0.60 sec. without loss of ventricular systole. With prolongations of the PQ interval of other origin than rheumatic fever one will get atrio-ventricular block with loss of ventricular systole already at lower values of PQ. Complete block in rheumatismus acutus has in Norse literature been reported among others by P. F. Holst, Salvesen, Anton Jervell, Folke Möller and Römcke. Steenström has described a case of complete block with endocarditis.

In the present material there is one case of second degree block of type 2 (case 1). In this patient a partial block was found at a

time, when the patient, as it was, had a tonsillitis, but where the articular phenoma, which besides had been moderate, had disappeared. The block was released by atropine (fig. 1).

It may be that one of the other patients had a complete block before he was warded in my department. This was a boy of 14 with aortic regurgitation, endocarditis and tonsillitis. The PQ interval in the electrocardiogram was 0.27 sec. One week before admission he had had a fit, during which he lost conciousness, but recovered soon again. Possibly this was an Adams-Stokes' attack.

In the literature several cases are described of rheumatic fever, where the disease started with a heart block, thus among others by Folke Möller and Römcke.

Disturbances of atrio-ventricular conduction are not only encountered in rheumatismus acutus but also in tonsillitis. Otto found electrocardiographic changes, e.g. increased PQ intervals, in 60 per cent. of patients who had suffered from acute tonsillitis, and Spreng a partial block of type 1. H. Laake reported previously from my department on tonsillogenous myocarditis. Among 15 patients with chronic tonsillitis a prolonged PQ interval was found in 3. It is, for the rest, emphasized by several authors, e.g. Holz, that the electrocardiographic changes in tonsillitis oftenest are observed after the acute stage is over. Ehlertsen mentions that the electrocardiographic changes in rheumatismus acutus sometimes persist for a considerable period of time after the temperature and sedimentation rate have become normal. Weicker points out, that the patients showing subjective symptoms, are those with disturbances of conduction.

What characterizes the electrocardiographic changes in acute rheumatism and tonsillitis is their transitoriness. This speaks in favour of the assumption that these changes are *functional* in nature and not due to true myocarditis. It lies close at hand to think of a toxic effect. Ruppert claims that toxines have a special affinity to the specific heart muscle fibres. A vagus effect must however not be left out of consideration. In case 1 the block was removed by atropine. In the case of P. F. Holst a complete block developed following an injection of digalen. After a subsequent injection of atropine the block was promptly checked. Slauck states that especially with toxic injury to the heart there is co-operation of the vagus. It seems therefore most natural to regard the disturban-

ces of A. V. conduction seen in rheumatismus acutus as being of partly toxic, and partly nervous origin (increased vagotonia), in such a manner *that the specific musculature of the heart becomes sensitive to the vagus by the influence of toxines.*

If we now go over to the cases of rheumatic heart diseases where the rheumatic infection long ago has passed away, we might think of several causes of the disturbances of A. V. conduction observed.

In 6 cases the cause might have been digitalis ordination. Of the 22 cases that were not treated with digitalis the size of the heart was studied roentgenologically in 19. In 4 of these there was no enlargement, in 6 there was slight, and in 9 considerable enlargement of the heart. In 2 of the latter cases there was hypertension above 200 mm Hg. Maybe the lengthened PQ interval found in these cases might have been due to an enlarged heart, e.g. in case 2.

It has been mentioned before that the bradycardia one often observes in patients with far gone mitral failure, both after digitalis and without, suggests that A. V. conduction is considerably impeded. These patients are sensitive to digitalis. In 2 of my patients with mitral stenosis and fibrillations I even observed the appearance of a complete block after relatively small doses of pandigal. In one of these cases the complete block developed after only 9 tablets containing 0.10 g digitalis. The block lasted 25 days. In the other patient the block appeared after 3 injections of strophantin and 5 pandigal tablets. The block however disappeared rapidly after few days. Also in a decompensated hypertonic with fibrillations a complete block developed after 4 ml + 4 tablets of pandigal, and lasted 8 days.

In the cases where no enlargement of the heart is to be found, and where the rheumatic infection took place several years ago, one must suppose that the prolonged PQ interval found is a residue of a previous infection. The functional, toxic disturbances of conduction in rheumatic fever are, as mentioned above, transient, and will in the majority of cases disappear after a short period of time. But in rarer cases a delayed A. V. conduction may be the residue of a previous infection (diphtheria, rheumatismus acutus etc.), what i. a. is mentioned by Korth (p. 241).

It is possible that a lasting functional toxic damage to the bundle of His form the basis of the partial block which I observed

in 2 cases with an enlarged heart cases 2 and 3. In case 2 there was first encountered a prolonged PQ interval of 0.30 sec, then a partial block with Wenckebach's periods, and then again a lengthened PQ interval, followed by auricular fibrillation arhythmia. The enlargement of the heart observed in this case may have been a concurrent cause of the partial block. Case 3 is rather exceptional: In a patient aged 29, who the last 10 years had been suffering from irregular heart action, but without dyspnea of work, a rather pronounced systolic murmur is found, and roentgenologically an enlarged heart and electrocardiographically a 2:1 A.V.block
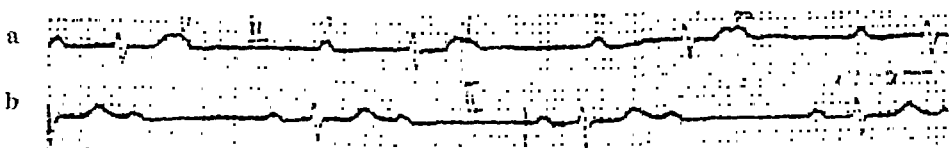
Fig. 2. R. O. W. ♂, aged 29. *Mitral regurgitation?* Electrocardiograms: a) Partial 2:1 block with PQ intervals varying from 0.32 to 0.56 sec. Sinusbradycardia. As the intervals between the QRS complexes are of varying length the block is not complete. b) After 1 mg atropine the heart beat becomes quite regular with PQ 35 sec. The PP intervals vary, the interval between the conducted P and the following one is shorter than the interval between the latter P and the subsequent conducted P (case 3).

(fig. 2). There was no anamnestic information as to any previous infection. As coronary sclerosis could be ruled out on account of the age of the patient, it was thought that a rheumatic infection might have injured the bundle of His, a functional partial A. V. block and mitral regurgitation (hypertrophy electrocardiogram) being the result. It seems less reasonable to assume that one had to deal with a congenital block in this case. One did not succeed to check the block by atropine, yet the PQ interval was somewhat shortened (v. fig. 2). The case illustrates that one should be careful with predicting an unfavourable course, if one finds an A. V. block in the electrocardiogram.

Luetic Heart Diseases.

The present material comprises 14 cases with positive serological reactions as to syphilis. Of these 5 had aortic regurgitation, 1 aortitis, 4 hypertonia and 4 lues latens (2 of these had ulcus duodeni). Of all these patients a roentgenray picture was taken, 6

having an enlarged heart. In 3 of the cases a complete block was found. One of the patients with complete block had also a bundle branch block. In this patient auricular fibrillations later developed.

In cardiovascular lues the characteristical electrocardiographical findings are alterations of the ventricular complex and of the T-waves, while a prolongation of the PQ interval is relatively seldom (v. Aastrup, p. 116). Holtzer and Polzer (p. 232) state that syphilis considerably less frequently causes disturbances of conduction than does acute rheumatic infection and diphtheria. The cause of the disturbances of conduction encountered in cardiovascular lues is usually ascribed to luetic infiltrations respectively older or cicatricial residual processes in the bundle of His.

If one leaves out of consideration the 4 cases of latent lues, it seems likely that changes of the kind mentioned formed the cause of the disturbances of conduction in the majority of the cases reported here. It is however possible that the enlargement of the heart may have been a concurrent cause in some of the cases.

Acute Infections.

If one in patients with acute infective diseases but without signs or organic heart disease finds a prolongation of the PQ interval in the electrocardiogram, it lies close at hand to correlate the electrocardiographical finding with the infection. In the present material are included 15 patients with acute infections (pneumonia, hepatitis), where a PQ interval of 0.22 sec. or more (maximum 0.25 sec.) was found, as a rule without other signs of pathological changes.

It seems reasonable to suppose that in these cases there had taken place a functional, toxic affection of the bundle of His, just as with rheumatic infections. It might be of interest to mention that in a number of these patients there was found eosinophilia, what might suggest an allergic reaction. In anaphylactic shock impeded A. V. conduction has been observed in animals (v. Lepeschkin, p. 417).

Focal infection must also be kept in mind, if one finds a prolonged PQ interval without known origin. Ruppert observed im-

paired A. V. conduction in 15 young individuals, who had not gone through any acute infective disease, the cause being, in the opinion of this author, a latent focal infection. Defocalisation in four of these cases was followed by complete recovery.

Hyperthyroidism and Hypothyroidism.

In this group 11 cases are classified, viz. 6 patients with Graves' disease and 5 with moderate forms of hypothyroidism. In 3 of the 6 patients with Graves' disease the impairment of A. V. conduction was probably due to digitalis. The PQ interval was found pro-
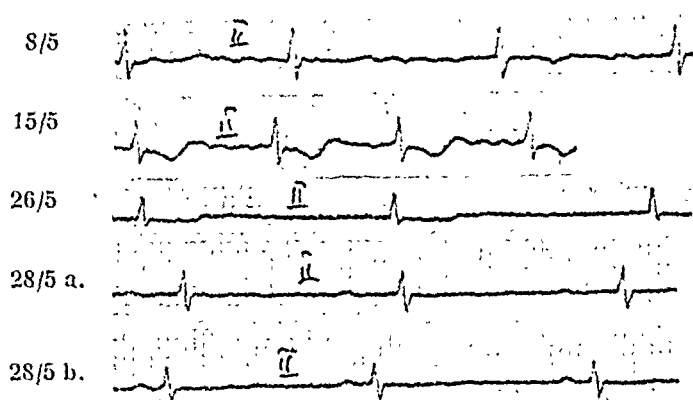
Fig. 3. I. M. G. ♂, aged 49. *Graves' disease.* Electrocardiograms: May 8. Auricular fibrillations. May 15. Effect of digitalis after 1.8 g folium Digitalis. May 26. Total A. V. block and auricular fibrillations. May 28. Sinus rhythm. PQ 0.33 sec. May 28. (after 1 mg atropine) PQ 0.17 sec. (case 4).

longed after heart action had become more regular subsequent to a fibrillatory arhythmia. In one of these patients (case 4) one week after strumectomy a complete block with retained auricular fibrillation developed under digitalis therapy. The heart rate by that time was regular, 44 fig. 3). To day later sinusrythm, — Pa = 0.33 sek. after 1 mg atropine 0.17 sec.

In another patient, a 20 years old man with Graves' disease, the PQ interval was 0.25 sec. before and 0.20 sec. after operation. This patient had not been treated with digitalis. Besides, the cholesterol content of the blood was remarkably low in this case, only 95 mg per 100 ml.

The patients with hypothyroidism showed highly varying figures for the PQ interval. In one patient, for instance, the PQ

interval decreased from 0.27 to 0.23 sec. during thyroid medication, while in another it increased from 0.20 to 0.24 sec. In a couple of the other patients during an observation time of several months values varying between 0.23 and 0.15 sec. were observed. In these patients there was however a tendency to reduction of the PQ interval during thyroid treatment.

The material presented here is by far too small to allow any conclusions to be drawn so far as regards the PQ interval in hyperthyroidism and hypothyroidism. At any rate there was not to be found any parallelism between the basal metabolic rate and the PQ interval. The cholesterol content of the blood may possibly be of some importance. Previous investigations (v. Lepeschkin, pp. 269 and 275) do not reveal any such congruity either. Lepeschkin is of the opinion that the heart rate and the exhaustion of the conductive bundle are factors of importance. Further investigations of this subject would be of interest.

Gastric and Duodenal Ulcers.

The commonest electrocardiographic findings in patients with peptic ulcers are the following: respiratory arhythmia, sinus bradycardia, high and acute T-waves (Draper et al., Nieuwenhuizen et al., Waider), and prolonged PQ intervals. If one includes all the cases with a PQ of 0.18 and more, one will find that A. V. conduction is considerably slower in patients with peptic ulcers than in healthy individuals, what has been emphasized by Draper and collaborators.

In the course of the last two years I have been able to observe PQ intervals between 0.22 and 0.27 sec. in 40 patients with gastric or duodenal ulcers. However, two of the patients suffered form hypertensive heart diseases, and two others from latent syphilis. In one patient the PQ interval was 0.37 sec. (repeated electrocardiograms), but this patient had previously had diphtheria, and had a doubtful diastolic murmur over the heart. It is therefore thinkable that the lengthened PQ interval found in this case was a residue of a previous infection (diphtheria or rheumatic infection).

The slowing of A. V. conduction is no doubt due to the action of the vagus. This explains also the fact, that the PQ intervals of

patients, where an electrocardiogram was taken repeatedly, not unfrequently showed varying lenghts. In one of these patients the PQ interval even was altered under deep respiration (from 0.20 to 0.23 sec.) After 1 mg atropine the PQ interval was shortened in the majority of the cases (v. table 4).

Functional Heart Diseases.

Prolonged A. V. conduction is found in a series of doubtful heart cases warded for observation. These patients display variegated symptoms, such as palpitations, sensations in the precordium, stenocardia, extrasystoles, etc. Not seldom these patients suffer from vaious digestive disorders, such as achylia, fermentative dyspepsia, spastic constipation, etc. The clinical diagnosis in these cases was: neurosis cordis, neurasthenia, syndroma gastro-cardiale, arhythmia cordis, paroxysmal tachycardia, etc.

In the 38 cases included in this group the PQ interval varied between 0.22 and 0.27 sec. A couple of these patients had not had any subjective symptoms, but had been warded for further examination because the physicians dealing with the cases had suspected an organic heart disease on account of a murmur heard over the heart, and extrasystole arhythmia. Thus a young lady, aged 22, was denied admission to a school of gymnastics because there was found a weak systolic, and certainly accidental, murmur over the heart, and on an occasional electrocardiographic examination a PQ of 0.22 sec. There was no enlargement of the heart. She was nevertheless admitted and took part in strenuous gymnastics without difficulty. On control examination one and a half year later the PQ interval was found to be 0.20. She had been tonsillectomized some time before the first examination. It is therefore possible that a tonsillitis was the cause of the impaired A. V. conduction observed.

Another example is the following: A 37 years old man went to a physician in order to get a health certificate. As the doctor found a systolic murmur and besides extrasystoles, the patient was referred to electrocardiographic examination. The electrocardiogram revealed a PQ interval of 0.27 sec., and a moderate bradycardia, the pulse rate being 52. In the atropine test (case 10 in table 4) the PQ interval was reduced from 0.26 to 0.18 sec. This patient

Table 4.

Length of PQ Interval before and after 1 mg Atropine in 20 Patients with Functional Disturbances of Conduction.

No.	Sex.	Age.	Disease.	PQ Interval Before Atropine.	After Atropine.
1	♀,	54 years	Ulcus ventriculi. Lues latens	0.22 sec	0.18 sec
2	♀,	40 »	Ulcus duodeni	0.23 »	0.18 »
3	♀,	46 »	» »	0.23 »	0.17 »
4	♀,	40 »	» »	0.23 »	0.15 »
5	♀,	67 »	» »	0.23 »	0.18 »
6	♂,	58 »	» »	0.24 »	0.25 »
7	♀,	54 »	» »	0.23 »	0.18 »
8	♂,	59 »	» »	0.22 »	0.19 »
9	♀,	18 »	Gastritis acida	0.22 »	0.18 »
10	♂,	37 »	Observatio	0.26 »	0.18 »
11	♂,	34 »	Dyspepsia nervosa	0.22 »	0.22 »
12	♂,	42 »	Observatio	0.26 »	0.18 »
13	♀,	49 »	»	0.23 »	0.18 »
14	♂,	39 »	»	0.25 »	0.18 »
15	♂,	53 »	Neurasthenia	0.24 »	0.20 »
16	♂,	41 »	Syncope	0.25 »	0.20 »
17	♂,	72 »	Tachycardia paroxystica	0.22 »	0.20 »
18	♀,	49 »	Morbus Basedowii	0.28 »	0.18 »
19	♀,	51 »	Pneumonia	0.23 »	0.18 »
20	♂,	62 »	Intoxicatio nicotini	0.23 »	0.16 »

was a sporting-man and had never shown any symptoms of cardiac disease. Neither had he had any previous infective diseases. On examination of the blood a slight eosinophilia (6 per cent.) was found. A latent allergic condition may possibly have been present. These two cases show that one should be careful with laying too much stress upon a single electrocardiographic anomaly.

In 8 cases gastro-cardial symptoms was present, thus in a woman of 32 with fermentative despepsy. She had for some time been suffering from palpitations and pains in the precordium, partly irradiating into the left arm. The PQ interval was 0.25 sec. After dietetic treatment the symptoms disappeared, and the electrocardiogram became normal with a PQ interval of 0.17 sec.

Syndroma gastro-cardiale was first described by Roemheld. He laid great stress upon a mechanical factor as the cause of

the cardiac symptoms, particularly a high position of the diaphragm as a consequence of gas-filled ventricle and colon. Salvesen emphasized that the symptoms mentioned are not seldom found in patients with general enteroptosis and achylia. The symptoms are of various kinds, such as extra systoles, palpitations, and angina pectoris (angina pectoris diaphragmatica).. Electrocardiographically often negative or flattened T-waves are found. In one of Salvesen's cases negative T-waves and PQ intervals of 0.20 sec. were observed. In my opinion a prolongation of the PQ interval is a symptom to be added to the gastro-cardiac symptoms. The cause of this electrocardiographic finding is possibly increased vagotonia, i.e. a viscero-visceral reflex.

Case 5 was also classified in this group in spite of a normal PQ interval of 0.20 sec. An increase of the PQ interval to 0.24 and 0.25 sec. was here only seen with beats following upon interposed ventricular extrasystoles. The case however shows some items of interest: The patient, a widow aged 38, was admitted to the department because she had fainted on several occasions without provocation. During one of the attacks the nurse attending her was not able to feel the pulse. On roentgenray examination a slightly enlarged heart was found. The pulse rate was somewhat slow, usually between 48 and 64, and once as low as 36.

The patient's fainting fits with non-palpable pulse make one think at once of Stokes-Adams' syndrome. Most of the cases of Stokes-Adams' syndrome are due to cardiac standstill caused by paroxysmal complete atrio-ventricular block, and more seldom to sino-auricular block (M. S. Andersen, Krarup, and others). However it is rather unfrequent that a complete block alternates with normal A. V. conduction (Comeau). Stokes-Adams' syndrome may also occur with paroxysmal tachycardia (Gallavardin, Wenckebach and Winterberg (p. 257), Zimmermann-Meinzingen, and others). Scherf (p. 221) even claims this form to be more frequent than the first mentioned one. With regard to the mechanism Scherf states: »that the stroke volume becomes the smaller, the faster the heart rate, i.e. the shorter the diastole. If the heart rate increases above a certain level, the time, that may be disposed for the filling of the ventricles, will become too short, the ventricles will throw out little blood and with so little energy, that the circulation practically stops.« It may however also come to a transitory

ventricular standstill as a consequence of ventricular fibrillations
of flutter. Zimmermann-Meinzingen was able to take electrocar-
diograms of a patient during fits of the kind. There was found a
reversible transition from ventricular flutter into ventricular stand-
still.

In our patient it may be doubted whether there existed any
organic heart disease inspite of the rather big heart. It is therefore
unlikely that the fainting fits were due to paroxysmal heart block.
Paroxysmal A. V. block will, at least in the majority of cases,
be caused by coronary sclerosis. It seems more reasonable to believe,
that the interpolated extrasystoles become so numerous, that paro-
xysmal ventricular tachycardia results with Adams-Stokes' syn-
drome.

Anemia.

In 12 cases there was found an anemia, which possibly may be
put into causative relation to disturbances of A. V. conduction
observed, with PQ intervals varying from 0.22 to 0.30 sec. However,
most of the patients were elderly people, so that coronary sclerosis
cannot be ruled out, all the more as no parallelism was found
between the degree of the anemia and the length of the PQ inter-
val. Thus the hemoglobin percentage increased in a man aged 54
with pernicious anemia from 43 to 88, while the PQ interval remain-
ed prolonged with alternating values between 0.22 and 0.24 sec.
In another man aged 53 with anemia after melæna the hemoglobin
was raised from 30 to 89 per cent., but in spite of that the PQ inter-
val remained long, varying between 0.26 and 0.30 sec. It is possible
that the anemia present in these cases is a concurrent cause of
disturbances of A. V. conduction in patients with slight arterio-
sclerotic changes. In a couple of cases vitamin B_1 deficiency might
have been a factor of importance.

In this group are also included two cases of *purpura*. Case 6
should be of some interest: A nurse aged 32 with thrombopenic pur-
pura and pronounced hemorrhagic diathesis has an attack of severe
retrosternal and epigastric pains. The electrocardigram taken
shows a lengthened PQ interval (se below under case reports). In
this case it is probable that a hemorrhage in the heart did affect the
bundle of His. Disturbances of conduction due to hemorrhage in
the myocard have been previously reported by Parade and Franke.

I found further a prolonged PQ interval of 0.23 to 0.25 sec. in a 73 years old man with purpura rheumatica. In the blood 165,000 blood platelets were found. However coronary sclerosis might possibly have been present in this case.

Discussion.

Atrio-ventricular conduction — finding its expression in the electrocardiogram in the PQ interval — will according to the majority of the authors of text-books normally require 0.12 to 0.20 sec. There are reasons to fix the upper limit at a somewhat higher level, e.g. 0.21 sec. (Larsen and Skulason). W. Schütz found among 100 healthy young men with no previous illness 3 who had a PQ interval over 0.20 sec.

Yet even if one choses 0.21 sec. for the upper limit of normal figures, one will not seldom find PQ intervals above this limit in people with sound hearts.

In the course of the last two years the author has treated 264 patients, in whom he found in the electrocardiogram, in at least one lead, a PQ interval of 0.22 sec. or more. Of these 187 (60 per cent.) suffered from organic heart disease. There is however reason to believe that the increased A. V. conduction time found in several elderly people without certain clinical signs of cardiac disease might have been due to sclerotic changes.

If a prolonged PQ interval is found in younger individuals the diagnosis in many cases may be difficult. To diagnose a »myocarditis» on the basis of a single electrocardiographic anomality, as for instance a PQ of 0.21 sec. would hardly be correct.

The disturbances of A. V. conduction due to organic or luetic heart diseases being left out of consideration, a prolonged PQ interval may be of different origin. Frequently an active rheumatic infection is to be found. But also other acute infections, such as tonsillitis, pneumonia, focal infection, or diphtheria are accompanied by disturbances of A. V. conduction.

What characterizes the electrocardiographic changes in acute infections is their transitoriness. This is in support of the view that one has not to deal with true »myocarditis». Atropine will in may cases release the block, as for instance in case 1, where a partial block, which had developed during a rheumatismus acutus with

tonsillitis, was checked by atropine. The majority of the authors agree as to the disturbances of A. V. conduction in acute infections being of functional, toxic nature. Ruppert claims that toxins have a special affinity to the conductive system of the heart. Much speaks in favour of the belief that the specific musculature of the heart under the influence of toxins becomes sensitive to the vagus. Post-infectious bradycardia points into the same direction. Digitalis has a similar effect. An atrio-ventricular block after digitalis is usually checked by atropine.

It is further likely that this parasympathetic hypersensitivity may last after the acute infection has passed. This might explain why the PQ interval remains prolonged in certain cases subsequent to an infection gone through (e. g. acute rheumatism, tonsillitis, diphtheria, etc.).

In several of my patients with an increased PQ interval I found a slight eosinophilia. A latent allergic state may be thought possibly to exist in these cases (vagotonia?)

Vagotonia may furthermore be the cause of a prolonged PQ interval in patients suffering from peptic ulcers, neurasthenia and gastrocardiac syndrome. Likewise increase of vagus tone has to be remembered if one finds an increased PQ interval in healthy subjects. W. Schütz mentions that he in an entirely healthy young man found a PQ of 0.23 sec. After bodily exertion (sympathetic preponderance) the PQ interval was reduced to 0.17 sec., and returned slowly to the original value of 0.23 sec.

The varying PQ intervals found in this material in hyperthyroidism may also be due to disturbances of conduction caused by the vegetative nervous system, though tachycardia may play a part.

Varying length of the PQ intervals is once and again found in patients with organic heart diseases. After 1 mg atropine the PQ interval is not seldom shortened (see table 3). This suggests that in organic heart disease there is a concurrent functional, nervous factor too.

In summarizing what has been said here, one may state that a prolonged PQ interval with a series of conditions may be ascribed to a increase of vagus tone. It is therefore probable that the conductive power of the bundle of His physiologically stands under the influence of the vegetative nervous system, especially the vagus. It is impossible to draw any sharp line between physiological

and pathological values for the PQ interval. In any case this would be a arbitrary borderline. If atropine is given the action of the vagus is abolished. One gets then the time it really will take the irritament to pass through the atrioventricular bundle without the inhibitory effect of the vagus. It would therefore be the most correct always to give the PQ values after 1 mg atropine. That this would be unpractical for clinical use is an other question. The upper limit of the normal PQ interval after atropine has of course to be

Table 5.

Length of PQ Interval before and after 1 mg Atropine in 10 Patients with normal Atrio-Ventricular Conduction.

No.	Sex	Age.	Disease	PQ Interval	
				Before Atropine	After Atropine
1	♂,	35 years	Ulcus duodeni	0.18 sec	0.18 sec
2	♀,	51 »	Tachycardia paroxystica	0.17 »	0.17 »
3	♂,	36 »	Extrasystole Arhythmia	0.20 »	0.18 »
4	♂,	47 »	Cholelithiasis	0.17 »	0.16 »
5	♂,	65 »	Pneumonia	0.19 »	0.16 »
6	♂,	50 »	Febris catarrhalis	0.17 »	0.16 »
7	♀,	66 »	Hypertonia	0.21 »	0.18 »
8	♂,	46 »	Tachycardia paroxystica	0.18 »	0.17 »
9	♀,	46 »	Hypertonia	0.16 »	0.15 »
10	♀,	63 »	Enteroptosis..................	0.17 »	0.16 »

fixed at a lower level than without. The pulse rate is not contained in the tables. It usually increased somewhat after atropin injections, though not enough to explain the reduction of the PQ values. Atropine given per os proved to be quite ineffective. The experiments are by far too few in number to allow any certain conclusions as to the normal PQ interval after atropine. The upper normal limit should probably be fixed at 0.18 or 0.20 sec. In table 4 are gathered experiments with patients without organic heart disease, and who had a PQ interval of 0.22 sec. and more. In a few cases there was no response to atropine. This may be due to the fact that the full effect of atropine possibly had not developed after one-half hour 15 minutes proved to be too short a time to give it. In table 5 we find experiments with individuals with normal A. V. conduction. The reduction of PQ is on an average less in this group. Further investigations on this line would be of interest.

In a previous paper (Jervell and Laake) the author has mentioned the possibility that an impairment of conduction in the bundle of His might be due to an *enlarged heart*. In the hypertrophic cardiac muscle blood supply is less satisfactory. It is therefore possible that a chronic coronary insufficiency might influence the blood circulation in the bundle of His. Besides it is possible that a pronounced dilation of the heart might *stretch* the conductive bundle, and thus affect its conductive power.

A rare cause of disturbances of atrio-ventricular conduction is a hemorrhage into the bundle of His in hemorrhagic diathesis (case 6). As possible concurrent causes of disturbances of conduction anemia and avitaminosis are mentioned.

The commonest cause of atrio-ventricular block nn doubt is coronary sclerosis and other cardiac diseases. In the present material these cases represent about 60 per cent. of the total number of cases examined. If one classifies the disturbances of conduction found in hyperthyroidism and hypothyroidism among the cases with a nervous causation, the latter represent 27 per cent. of all cases, In these cases it is, as a matter of fact, more correct to speak of impairment of conduction. To the functional, toxic cases 9 to 10 per cent. may be counted. In the remaining 3 to 4 per cent. with a prolonged PQ interval the pathogenesis is less clear.

One finds thus that disturbances of A. V. conduction or impairment of conduction are frequently to be seen, also in healthy individuals. There should therefore not be laid to much stress upon one single electrocardiographic anomaly, such as a prolonged PQ interval. This like the other electrocardiographic findings have to be valuated on the basis of the clinical picture as a whole. Even a partial block may be functional in nature (case 3).

The diagnostic difficulties may in certain cases be great, not at least in patients with a series of »nervous» symptoms, such as palpitations, extrasystoles, angina pectoris gastro-cardiac symptoms, dyspnea, etc. The dyspnea which these patients complain of is not a working dyspnea; in cardiac and respiratory neurosis respiration is often superficial with paroxysmal air-hunger (Heckscher).

Summary.

A clinical material has been studied in order to find out how frequently functional disturbances of atrio-ventricular conduction occur.

The author hes in the course of the last two years examined 317 patients disturbances of atrio-ventricular conduction (PQ = 0.22 sec. or more). 10 of these patients had a complete block, 12 a second degree block, and the remaining 295 a prolonged PQ interval without loss of ventricular systole.

Among the degenerative cardiac diseases 146 cases are classified, 4 of which had a complete block, and 7 a partial block. 9 patient had cardiac infarctions. 6 patients had besides the atrio-ventricular block also a sino-auricular block, and 24 had a bundle branch block.

Of rheumatic heart diseases with disturbances of atrio-ventricular conduction 43 cases were observed, whereof 15 were in the acute respectively subacute stage. In 3 cases there was a partial block (cases 1, 2, and 3).

The material comprises 14 cases with positive serological test for lues, 3 having a complete block.

In 15 cases the probable cause of the disturbances of conduction were acute infections (pneumonia, hepatitis, etc.).

An increase of the PQ interval was found in 11 patients with hyperthyroidism and hypothyroidism respectively.

In 40 patients with ventricular or duodenal ulcers a prolonged PQ interval was seen, and besides in 38 patients with nervous cardiac symptoms, gastrocardiac symptoms, or in patients warded for observation suspect of heart disease. In 12 cases anemia was present. In one case of thrombopenic purpura with stenocardiac attacks, a hemorrhage into the myocard was probably the cause of the disturbance of A. V. conduction observed.

In 60 per cent. of the cases it is assumed that organic heart or vascular disease was the cause of the atrio-ventricular block found, in 27 per cent this was probably of nervous origin, (vagotonia) and in 9 to 10 per cent. functional, toxic of nature. It is assumed that the specific muscle fibres become sensitive to the vagus by the action of toxines. The inhibitory effect of the vagus on the bundle of His is discussed.

It is pointed out that cardiac enlargement may be the cause of disturbances of atrio-ventricular conduction in certain cases.

Case Reports.

Case 1. *Rheumatismus acutus, tonsillitis, partial block.*

E. O. H., woman aged 28. Several years ago angina, followed by acute appendicitis. After appendectomy she got a rheumatic fever. The electrocardiogram was normal then.

On April 1, 1942 she got again an angina. Short time afterwards swelling and pains developed in a series of joints. She did not take the temperature, but probably had fever. She went to bed, and after come weeks the articular phenomena disappeared. Pat. was admitted to the hospital on May 1.

On admission there was no swelling of any joint, and full movability of all the joints.

The tonsils were enlarged and clefted. Detritus and a purulent fluid could be pressed out of them.

Over the heart a not very pronounced systolic murmur with its punctum maximum over the apex could be heard, as well as a protodiastolic gallop.

The sedimentation rate was 115 mm.

The roentgenogram showed no enlargement of the heart shadow.

An *electrocardiogram* (fig. 1), taken few days after admission, showed a partial block (type 2). The following two electrocardiograms showed a first degree block with considerably increased A. V. conduction, viz. 0.40 and 0.38 sec respectively. The patient received now 0.25 mg atropine 4 times a day for 6 days, and on the seventh day besides an injection of 0.75 mg atropine. Immediately after this an electrocardiogram was taken, chowing entirely normal findings with a PQ interval of 0.19 sec. The sedimentation rate at the same time having dropped from 110 to 60 mm, and the temperature having become almost normal, we decided, after having consulted a specialist, to perform tonsillectomy (May 18). The electrocardiogram taken the day after was normal with a PQ of 0.17 sec On the second day after operation there came a rise of temperature, the heart rate at the same time increasing, and pains and swelling developed in all the big joints, especially the left knee and the right wrist. The sedimentation rate rose to 110 mm. An electrocardiogram taken two days after tonsillectomy showed tachycardia. As the T and P waves in the electrocardiogram coincide an account of the accellerated heart action it was difficult to determine the length of the PQ intervals exactly, but this was about 0.30 sec. It lasted quite a time are the articular symptoms decreased. Except a somewhat accellerated heart action during the first days after operation, the patient had no cardiac symptoms. The patient was dismissed on July 10, symptom-free and with a normal electrocardiogram, the sedimentation rate still being 60 mm though.

Case 2. *Mitral stenosis, partial block.*

K. S., man aged 30. Had not had rheumatic fever. The last 2 to 3 months he had had dyspnea of work.

Blood pressure 120/80 mm Hg. Meinicke's reaction negative.

Over the apex of the heart a rolling presystolic crescendo murmur and a snapping first sound was heard.

The roentgenogram showed an enlarged, muscle configurated heart. Internal thorax diameter: 30 cm; Tr: 15.5 cm.

Electrocardiogram: June 27, 1942: Right preponderance, high and acute P waves. PQ 0.30 sec. ST_2 and ST_3 are lowered (no digitalis treatment). June 29, 42: Partial A. V. block, type 1. July 3, 42: PQ 0.25 sec. Aug. 24, 42: Fibrillary arhythmia.

Case 3. *Mitral regurgitation(?), partial block.*

O. O. W., man aged 29. 9 years old acute appendicitis. Had not had rheumatic fever. During the last 10 years the heart beat had been irregular, the patient otherwise feeling quite well. He had not had dyspnea of work, cyanosis or edema. He had been smoking heavily (cigarets) all these years. During the last year, after he had stopped smoking, he had noticed that his heart had become more regular, and that the heart rate at the same time had become strikingly slow.

Status praesens on April 12, 1943:

BP 130/75 mm Hg. Pulse rate 50, regular.

Heart: Dullness 3rd costa — left sternal margin. Ictus cordis in the 6th intercostal space, inwards of the medioclavicular line. Over the whole heart a systolic, slightly sawing murmur is heard, most distinctly at the left sternal margin at the level of the 4th rib.

Blood: Hb. 92 per cent. SR 6 mm. Meinicke's reaction neg. Total cholesterol: 205 mg per 100 ml.

Roentgenogram: The heart shadow seems to be large, though it is not increased compared with the internal thorax diameter (Th/Tr 32.2/16.5 cm)

Electrocardiogram: see fig. 2.

Case 4. *Graves' disease. Fibrillation arhythmia, complete block.*

I. M. G., woman aged 49. No previous diseases. The present disease started about one-half year ago with dyspnea of work and palpitations, particularly when mounting stairs. Loss of weight. Noticed enlargement of her neck. Frequent diarrheas.

Status praesens, April 24. 1941:

Patient stares fixedly. There is marked protrusio bulborum. Graefe's sign and Stellwag's sign are positive, Moebius' sign negative. There is distinct tremor manuum et linguae.

Pulse rate 80, regular. Blood pressure 135/65 mm Hg.

Heart: The ictus cordis is powerful, and found in the 5th intercostal space in the medioclavicular line. Over the whole heart a rather pronounced systolic murmur is heard. The 2nd pulmonary sound is accentuated.

Diffuse enlargement of the thyroid gland.

Blood: SR 9 mm Hb. 95 per cent. Erythrocytes 5.07 mill.

Urine: Alb. —, Blood —, Sugar —.

BMR: 186 per cent.

Electrocardiogram: see fig. 3.

From May 1. the patient was treated with digitalis, 0.1 g 3 times dayly for 6 days, and thereafter 0.1 g once a day, and Lugol's solution, 5 drops thrice a day. Thyroidectomy on May 12. Rise of temperature to 39.7° C, otherwise the course was uncomplicated. The basal metabolic rate after the operation, 1 week later, was 87 per cent.

Case 5. *Arhythmia cordis. Stokes-Adams' syndrome. Obstipatio spastica.*

I. S., woman aged 38. 3 children, one of whom has asthma, the two others are healthy.

In 1918 — 17 years old — the patient had a serious influenza. She had then attacks of dyspnea, had to sit up in her bed in order to be able to recover her breath. In 1937 she was pregnant, pregnancy ending with stillbirth. During pregnancy there was proteinuria and edemas. After birth she was suffering from stiffness of both knees, which improved after a cure.

When her husband died in 1938 she had much work to do and many troubles. She thinks that she over-worked herself. She frequently fainted during the menstruation. On Jan. 16, 1939 she felt quite unwell in the morning. Early in the forenoon she suddenly dropped on the floor, but did not faint. Patient had herself the impression that heart stopped. A nurse, who was present was not able to feel any pulse. Shortly afterwards she was able to rise to her feet and to go up one pair of stairs to her room. Later she has fainted several times.

Patient has been somewhat dyspnoic.

Her doctor states that the patient's pulse rate may be very slow, 40 to 52, and quite irregular.

Status praesens, Jan. 18, 1939:

Patient is a rather stout woman.

Pulse rate 52, regular. Blood pressure 120/70 mm Hg.

Heart: No absolute dullness. Normal sounds.

Lungs and abdomen: Nothing special.

Urine: Normal.

Blood: Meinicke's reaction negative. SR 11 (later 6) mm Hb. 83 per cent. Erythrocytes 4.17 mill. Colour index 1.00.

During patient's stay at the hospital her pulse was oftenest irregular, rather varying of nature, once as low as below 36, usually however between 48 and 64.

Roentgenogram: Slightly enlarged heart. Internal thorax diameter: 27 cm, Tr. 14 cm.

Electrocardiogram: (Jan. 19) Regular sinus rhythm. PQ 0.20 sec. Heart rate 77.

Jan. 30: Interpolated extrasystoles. PQ 0.16 sec, and after extrasystoles 0.27—0.26 sec.

Febr. 6: Interpolated extrasystoles. 30 min. after 0.75 mg atropin no extrasystoles, PQ 0.20 sec.

June 23, 42: She faints frequently, drops suddenly on the floor. She

may walk in the street, and suddenly fall without premonition. Some dyspnea, when going up hill.

Electrocardiogram: Interpolated extrasystole. PQ 0.20—0.24—0.26.

Case 6. Purpura thrombopenica, first degree block.

A. M., woman, born Oct. 16, 1909.

In 1932 the patient was treated for menorrhagia in the Telemark County Hospital. In 1934 she was warded in the Porsgrund Hospital for an intestinal hemorrhage. A thrombopenic purpura was diagnosed. In 1937 tonsillectomized on account of chronic tonsillitis. During many years she had suffered from cutaneous hemorrhages in the form of blue and green patches up to the size of a palm of the hand. These hemorrhages appear without any trauma. Menstruation has often been copious and of long duration. In 1939 a blood examination revealed 48700 blood platelets, Hb. 85 per cent., erythrocytes 4.13 mill., colour index 1.03, leucocytes 7800. The bleeding time was 8 min. and coagulation time 5 ½ min. Later blood examinations showed 2300—40000 blood platelets. In 1940 she had an attack of severe retro-sternal pains. The pain was releaved after a few minutes.

Status praesens, May 31, 1940:

Pulse rate 72, regular. Blood pressure 115/80 mmHg.

Heart: Dullness 4th rib — left sternal margin. The ictus cannot be felt. Over the whole heart a short and soft systolic murmur is heard with its punctum maximum over the apex.

Blood: Hb 90 per cent. Erythrocytes 4.4 mill. Colour index 1.02. Leucocytes 7800.

0 0/ 0 1 13 39/46 9

Few blood platelets in the smear.

Bleeding time 9 min. Coagulation time 1 min.

Blood platelets 31,000.

Sternal puncture: The marrow is very poor in cells, these being mainly myelocytes, and only a few megakaryocytes.

June 6, 1940: Patient had a fit of cramplike pains in the epigastrium and the precordium. No dyspnea during the fit.

Electrocardiogram June 6: PQ = 0.25, otherwise normal. Positive T-waves in all the leads.

June 13: PQ = 0.26, otherwise normal.

June 19: PQ = 0.20. Positive T-waves in all the leads.

June 24: PQ = 0.24 otherwise unchanged.

June 25, 1940: Splenectomy.

July 5, 40: Blood platelets 64,000.

July 8, 40: Roentgenray picture of thorax: negative findings.

July 8, 40: Electrocardiogram: PQ = 0.20 sec.

July 15, 40: » : PQ = 0.19 »

Blood platelets 189,000.

Aug. 5, 40: Electrocardiogram: PQ = 0.16 sec.

Sternal puncture. Marrow rich in cells. Megacaryocytes are found all over the smear.

Febr. 1, 41: Electrocardiogram: PQ = 0.22 sec, otherwise normal.

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Electrocardiographic Examination of Orthostatic Hypotension in Hypertensives before and after Sympathectomy.

By

SVEN HAMMARSTRÖM.

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This study is part of an examination of hypertensives operated upon by Professor H. Olivecrona at the Neuro-Surgical Service of the Serafimer Hospital in Stockholm. The patients were sympathectomized according to Peet or Smithwick. According to Peet the three lower dorsal sympathetic ganglia and the roots of the splanchnics were extirpated, according to Smithwick the four lower dorsal ganglia, the first lumbar ganglion and the roots of the splanchnics.

Electrocardiographic examinations were performed pre- and postoperatively at St. Erik's Hospital. Most patients have been examined up to 2 ½ years after sympathectomy.

Pathologic electrocardiographic changes registered in recumbent position have shown a tendency to disappear postoperatively. In some patients electrocardiographic changes such as inverted T-waves appeared after sympathectomy, but these changes disappeared after a week.

Apart from the drop of blood pressure in hypertensives in recumbent position after sympathectomy there is an orthostatic fall of blood pressure accompanied by a more or less pronounced acceleration of the pulse rate. The more extensive the sympathectomy the more pronounced the orthostatic disturbance. The first weeks

after the operation according to Smithwick this disturbance usually is so great that the patients faint when trying to rise. This pronounced orthostatic insufficiency of the circulation disappears after some weeks, and none of our patients have had any complaints of this kind for a longer period than four months. This is in accordance with Smithwick's own findings. Most patients have presented a more pronounced orthostatic fall of blood pressure during the whole postoperative observation period than before the operation. After stabilization of the postoperative situation the orthostatic hypotension as a rule is not accompanied by the marked tachycardia of the first weeks. I have earlier put forth evidence for the belief that this remaining orthostatic hypotension is a favourable effect of the operation (3).

Table 1.

	Pulse rate per minute	Blood pressure in mm Hg		T-waves height in mm.		
		Systol.	Diastol.	Lead I	Lead II	Lead III
Means for 14 preoperatively examined and 6 non-operated hypertensives.						
Recumbent	77	195	120	1.10	1.43	0.39
Change in Erect position	+16	—23	—3.4	—0.26	—0.03	+0.2
Means for 35 normal persons according to O. Nordenfelt.						
Recumbent	74.0	125.0	81.4		4.03	1.69
Change in Erect position	+12.4	—6.3	+5.0		—1.11	—0.71

Electrocardiograms were taken in recumbent and erect position before and after sympathectomy in order to illustrate how the orthostatic changes affect the heart. The examinations were carried out on a tilting table and the registration in erect position was made after the patient had been standing for about five minutes. In the cases, where the orthostatic hypotension was most pronounced, the electrocardiographic record had to be made immediately after the patient hade been tilted to erect position. Determinations of blood pressure and of pulse rate were made every two minutes during 10 minutes in recumbent and erect position. The values recorded in immediate connection with the electrocardiograms are given in the tables.

Table 2.

Results from tilting tests on 14 hypertensives after sympathectomy according to Peet or Smithwick.

	Time after sympathectomy	Age Years	Blood pressure			Pulse pressure	Pulse rate Beats per min.	T-waves Height in mm in lead			S—T Height in mm in lead	
				Systol.	Diastol.			I	II	III	I	II
Women												
M-n	3 weeks Smithw.	44	Recumb.	120	75	45	66	2	4	2		
			Erect.	50	0	50	112	2	1.5	—1	—0.5	—1
R-th	12 m-ths Peet	58	Recumb.	175	110	65	88	2.5	1	—1.5	0	—0.5
			Erect.	120	85	35	116	4	2	—2	0	—0.5
T-n	3 weeks Smithw.	36	Recumb.	235	140	95	64	0.5	1	0.5	0	0
			Erect	95	70	25	108	1.5	3	1.5	0	0
T-en	2 weeks Smithw.	43	Recumb.	135	95	40	88	2	2	0	0	0
			Erect.	80	60	20	130	2	2.5	0	0	0
S-d	19 m-ths Peet	50	Recumb.	135	90	45	84	1.5	4	2.5	0	1
			Erect.	90	70	20	116	2.5	4	1.5	0	1
S-m	3 weeks Smithw.	41	Recumb.	160	110	50	75	1.5	2.5	1	0	0
			Erect.	100	75	25	150	1.5	2.5	1	—0.5	0
P-n	3 weeks Smithw.	50	Recumb.	165	110	55	96	1.5	4	2.5	0	0
			Erect.	115	65	50	128	1.5	4	2.5	0	0
B-f	3 m-ths Smithw.	44	Recumb.	180	130	50	80	2	3.5	1	0	0
			Erect.	135	115	20	110	1	4	2.5	0	0
Men												
B. M-r	3 weeks Smithw.	21	Recumb.	135	110	25	108	2	4.5	2.5	0	0
			Erect.	50	50	20	145	2.5	6.5	5	1.5	1.5
W-g	3 weeks Smithw.	55	Recumb.	125	95	30	60	2	1	—0.5	0	0
			Erect.	75	65	10	98	1	1	—0.5	0	0
Å-n	3 weeks Smithw.	45	Recumb.	150	90	60	92	1	1.5	1	0	0
			Erect.	90	60	30	150	1.5	4	2	—1.5	—1
L-m	3 m-ths Smithw.	39	Recumb.	145	110	35	72	3.5	2	—0.5	0	0
			Erect.	105	85	20	142	—0.5	1	1.5	0	0
W-g	11 m-ths Peet	48	Recumb.	170	115	55	76	0	2	2	0	0
			Erect.	120	95	25	122	0	1	1	0	0
J-n	8 m-ths Smithw.	41	Recumb.	205	130	75	72	0	1	1	0	0
			Erect.	145	115	30	120	—0.5	1.5	1	—0.5	—0.5

The untreated patients when raised to erect position as a rule show a systolic fall of blood pressure of 10 to 20 mm Hg, while the other half show an increase of about the same order. The orthostatic acceleration of the pulse rate varied in these patients between 8 and 22 beats per minute. One patient showed no orthostatic accele-

ration of the pulse, while two others presented an acceleration of the pulse rate of 33 to 40 beats per minute without any pathologic hypotension. Some untreated hypertensives showed an orthostatic fall of blood pressure of 70 mm Hg systolic and 20 mm Hg diastolic without accompanying tachycardia. There is reason to believe that such sympathetic insufficiency is of practical significance for elderly persons.

There is in no case of the untreated patients any pathologic lowering of the T-waves in erect position. In three of them there was in erect position a lowering between 0.5 and 1 mm of the S—T segments in leads II or III. In Åkesson's normal material 14 per cent had a lowering of S—T in lead III of mean 0.77 mm (6).

In Table 2 are put together the results of the orthostatic determinations of 14 hypertensives who after sympathectomy showed marked hypotension. Only one of the patients, a 44-year-old woman of vasolabile type, did show significant pathologic electrocardiographic changes of the type developing in arterial orthostatic anemia. This patient showed no orthostatic disturbance or electrocardiographic changes before the operation. Neither in this patient nor in the others, where pathologic orthostatic electrocardiographic changes were lacking, was there any clinic support for coronary insufficiency in connection with the orthostatic hypotension. In spite of the pronounced orthostatic disturbance electrocardiograms in recumbent and erect position show remarkably small variations.

In Table 3 are put together the average values from Table 2 and average values from corresponding determinations on sympathectomized hypertensives, who showed less marked orthostatic disturbances after the operation than the previous group. As a comparison I quote in the same table from Nordenfelt (9) the means of the same determinations of 21 cases of arterial orthostatic anemia. Åkesson in about half of his cases with arterial orthostatic anemia found a lowering of S—T in leads II and III of mean 1.57 and 1.44 respectively. Of the 34 patients examined postoperatively in Table 3 eight in erect position presented a lowering of S—T in lead II of between 0.5 and 1 mm — mean 0.75 mm — and six showed lowering of S—T in lead III of mean 0.67 mm. In three cases an elevation of between 0.5 and 1.5 mm of S—T in leads II and III appeared. Åkesson found a lowering of T: III of mean

Table 3.

	Pulse rate Beats per minute	Blood pressure mm Hg		Pulse pressure mm Hg	T-waves height in mm		
		Systol.	Diastol.		Lead I	Lead II	Lead III
Means for 14 sympathectomized hypertensives according to Table 2.							
Recumbent....	81	160	108	52	1.57	2.46	0.96
Change in erect position	+45	—72	—38	—24	—0.14	+0.29	+0.11
Means for tilting tests on 20 other sympathectomized hypertensives.							
Recumbent....	80	185	118	67	1.40	1.96	0.43
Changes in erect position	+21	—35	—18	—17	—0.30	—0.35	+0.03
Means for 14 cases of arterial orthostatic anemia according to O. Nordenfelt.							
Recumbent....	81.3	122.9	81.4	41.5	—	2.74	1.16
Changes in erect position	+34.9	—11.8	+5.7	—17.5	—	—2.39	—2.39

3.33 ± 0.44 mm in erect position in arterial orthostatic anemia and observed that there was a statistically proved correlation between this lowering and the acceleration of the pulse rate and the fall in pressure. Such correlation does not exist in the orthostatic disturbances after sympathectomy. Åkesson found an inversion of T: III in erect position in 48 per cent of the cases with arterial orthostatic anemia. This has not been observed in any of the orthostatic changes I studied.

In the analyses of hypertension the so-called nitrite-test is included. Six doses of 0.032 g sodium nitrite are given per os with half an hour's interval. Immediately after the nitrite-test the patients were examined orthostatically on the tilting table as described before. S. Weiss and his collaborators found that about half the normal persons after the corresponding nitrite dosage developed an orthostatic collapse of circulation while in the other half the orthostatic regulation was not affected. I have found the same to be the case for hypertensives. The effect of the nitrite is considered as peripheral (10). The cause of the varying effect of nitrite in erect position is unknown. I have not been able to observe that the body-build is of any importance for appearance of the orthostatic

Table 4.

	Pulse rate beats per minute	Blood pressure mm Hg		Pulse pressure mm Hg	T-waves Height in mm		
		Systol.	Diastol.		Lead I	Lead II	Lead III
Means for tilting tests after nitrite tests on 17 hypertensives including 8 examined after sympathectomy.							
Recumbent....	80	144	93	51	1.16	2.15	1.16
Change in erect position	+41	—64	—34	—30	+0.32	+0.68	+0.39

nitrite collapse. After extensive sympathectomy according to Smithwick the blood pressure-lowering effect in a few cases was so pronounced even in recumbent position that the test had to be interrupted. In the other hypertensives the nitrite-test gave a moderate and rather constant hypotension in recumbent position. No electrocardiographic changes did appear in recumbent position. Table 4 gives the results of the orthostatic determinations during the effect of nitrite in 17 hypertensives, in which the orthostatic fall of blood pressure was most strongly pronounced. Eight of these patients were examined after sympathectomy. The orthostatic hypotension after the nitrite-test was accompanied by an acceleration of the pulse of between 16 and 90; average 40.8 beats per minute. In the patients presenting the greatest acceleration of the pulse rate a heightening of the T-waves in all leads appeared in erect position. In one case there was after nitrite collapse a slowing of the ventricular rate from 62 to 55 beats per minute due to a transitory block (2nd degree's block). Also in connection with this a heightening of the T-waves in all leads appeared. Such orthostatic electrocardiographic changes as in arterial orthostatic anemia did not develop during nitritecollapse in hypertensives except in one patient examined after sympathectomy. Even without nitrite this patient showed such orthostatic electrocardiographic changes. No principal differences between operated and non-operated hypertensives have been observed in the electrocardiograms in erect position during nitrite collapse.

Åkesson interpretes the electrocardiographic changes in erect position appearing in arterial orthostatic anemia as an expression

of coronary insufficiency. Against the background of such a belief it is remarkable that electrocardiographic changes of that same kind do not appear in marked orthostatic fall of blood pressure in hypertensives. Postural hypotension is a syndrome characterized by orthostatic collapse without acceleration of the pulse rate due to the non-existence of the sympathetic vascular reflex. According to an observation of Lindgren and myself this defect may be centrally conditioned (5). As the electrocardiographic changes characteristic of arterial orthostatic anemia do not appear in postural hypotension Ewert did not accept the interpretation of Åkesson and interpreted the changes as an expression of increased sympathetic tone. Nordenfelt reached the same conclusion by proving that the orthostatic electrocardiographic changes disappear under the influence of ergotamine. Åkesson rejected the objections of Ewert and Nordenfelt by pointing out that the non-appearing electrocardiographic changes under the influence of decreased sympathetic tone may be explained by a reduced dynamic work of the heart as shown for instance in the reduced pulse rate (7).

In the orthostatic collapse appearing immediately after extensive sympathectomy in hypertensives there is a greater fall of blood pressure than in arterial orthostatic anemia, an equally great reduction of pulse pressure and a more pronounced acceleration of the pulse rate. Neither anatomic nor physiological findings suggest that sympathetic ganglia or nerves enervating the heart are touched by the operations according to Smithwick or Peet. The great compensatory acceleration of the pulse rate during the orthostatic hypotension also indicates, that the sympathetic enervation of the heart is intact.

Young, healthy persons with arterial orthostatic anemia show pronounced electrocardiographic changes, while such changes under similar conditions are lacking in hypertensives, many of whom earlier have shown signs of failing heart action. This demonstrates the difficulty in appraising the coronary circulation from electrocardiographic examinations.

Summary.

Electrocardiographic examinations of hypertensives in recumbent and erect position were made before and after sympathectomy. Special attention has been given to electrocardiograms recorded during impending orthostatic collapse after sympathectomy or after doses of sodium nitrite. In some cases orthostatic hypotension was observed in untreated hypertensives. This material is compared with electrocardiographic examinations in arterial orthostatic anemia made by previous investigators. The typical orthostatic changes appearing in electrocardiograms from patients suffering from arterial orthostatic anemia are not present in orthostatic hypotension of hypertensives.

The present study is a contribution to the discussion of the nature of orthostatic electrocardiographic changes.

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Pallido-striatic Symptoms in War Psychosis.

By

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The war has brought about many psychic diseases, but none have caused a greater interest than the so called war hysterias. Neither the layman nor the surgeon can avoid being gripped by the sadly absurd symptoms of confusion, lameness, stupor, sillyness, dumbness, deafness, blindness, trembling, stuttering, spasms, tics, etc. that these psychosis of war terror produce.

When discussing their origin one has not always felt inclined to call them hysteria, as it may be somewhat precarious to draw a line between »natural» reactions of fright and such reactions that may be called an ailment, and it may also be difficult to define and to limite the meaning of the term hysteria.

Hysteria has been called »an escape into illness», »a desire for illness», »opportune neurosis», »Zwecksneurose», etc. Alfen calls hysteria »the psychic illness, the symptoms of which have been created by the desire to demonstrate these symptoms to the surroundings». Yet I think it may be agreed upon that the central point of hysteria is the hysterical splitting of the mind, the division of personality. The inner strength of the ego that is a characteristic of the normal person is loosened in the hysterical man. He lacks the associative inhibitions that join the various components of the mind and unite body and soul.

The horrors of the war may cause a splitting of the mental life. »Higher» action, governed by associative inhibitions and by power of will may give way to a more primitive »action by instinct» dominated by simple, unimpeded impulses of the will and by emotions. In this meaning »war hysteria» is a hysterical reaction.

This splitting of the mental life must, theoretically, be possible in every being and a number of psychiatrics consider in fact, that every man may react hysterically. Evidently some persons succumb to hysteria much more easily than others do. Children do, and primitive peoples, and *persons that according to Sjöbring are subsolid,* and in whom the balance and harmony between the various components of the psychic are not so strong and looser than among others. They have a more mobile mental life because emotions and impulses are not so closely connected with thought and will and thus have a more independent power of reaction. This psychic infantilism may be coupled with debility or imbecility and has something of the child's affectability with superficial, hastily changing moods and general unreliableness. They often belong to families with psycho-pathological inheritance and are called »nervous» and »unbalanced» or, are said to have »bad nerves».

Many attempts have been made at reaching a more profound understanding of the mechanism of the origin of hysterical reactions. So has Gadelius, but the theory he has brought out must be placed in a class of its own. It is as follows:

In the phylogenetic development of the nervous system, the cerebellum system was built up above the simple system of reflex arcs in the spinal cord, and above it the extrapyramidal system, consisting of a thalamus as a centre for the pallidum and the striatum. Above all this the cerebral cortex was finally developed.

In the extrapyramidal system the phylogenetically older pallidum distributes the effect of the agonists and antagonists very rationally, while the younger striatum controls the more complicated movements that, with constant changes, are used in our vegeto-animal adjustment to the outside world. In the animal world we notice that motoric and psychomotoric occurrences follow side by side with the development of the brain in developments from lower stages to higher ones. The primitive palaeostriatum of fishes is analogous to the pallidus in superior animals. The mouth is the only gripping organ and the movements in the water are a simple

reciprocal action between agonists and antagonists. Conditions are more complicated among the amphibians already. Their striatum is a superior centre and hereby the more and more complicated movements of the developing extremities are made possible. The ability to sit, to stand and move in an upright position is connected with a further development of the striatum and of certain centres in the cerebral cortex.

In superior animals and in man the guiding of the movements has thus »wandered» from lower centres to higher ones. This does not, however, imply that the lower centres have been evacuated. On the contrary, they still seem to harbour just these primitive movements. This is disclosed in a striking way in the human pathology, when in abnormal changes in the extrapyramidal system disturbances in the motor area appear in the form of »paleostriatic» symptoms. These symptoms appear very clearly in the »Parkinsonism», »paralysis agitans», »chorea», »atetosis», »rigidity», tremor, difficulty to move, mask-like face, stupor, etc. of the Economo-encephalites. They appear when the central ganglions have been deducted, during the illness, from the control of the cerebral cortex, when the normal cooperation between the cerebral cortex and the central ganglions has been broken off. The central ganglions have attained a certain autonomy of those primitive movements that they direct but the cerebral cortex controls.

Gadelius considers that the mental occurrences are similar to the motoric. In animals, with undeveloped cerebral cortex, the psychic events must take place in the pallidostriatic-thalmatic system, but a wandering towards higher centres takes place in higher stages of development. The cerebral cortex finally becomes the organ which in the form of a structure above the lower centres prepares the way for consciousness of matter, thought and superior differentia of will in man. It is not said, hereby, however, that impulse, instinct and desire have moved into this upper floor and have abandoned their former abode in the subcortical ganglions. When the human embryo is fully developed the functional instrumentation of the cerebral cortex has hardly been started. The newly born child is a »thalamus-pallidum-being». The ripening of the cerebral cortex and the reciprocal action between it and the subcortical ganglions is completed later, and not until after puberty does the ego attain its inner and outer firmness which characterizes

the adult. And yet the newborn child possesses psychic qualities atleast such as power of will, desire and impulse, and it seems exorbitant to believe that these psychic processes move into the »upper floor», later on, leaving the subcortical ganglions empty. Gadelius maintains that the subcortical ganglions remain the »site of the animal mind», an organ or instrument for impulse, need and affect that is awaked by contact with the outside world, and for the movements that the animal adaption for the outside world requires.

He believes that in some states of disease certain psychic symptoms are accounted for by the central ganglions having retaken some of their animal independence. The akinetic and hyperkinetic disturbances in movements, in processes in the subcortical ganglions, are often accompanied by typical psychical changes. They refer principally to will, feeling and impulse. The spontaneity, intentions, attentiveness and psychical views of the diseased is either inhibited, or else strongly affectations deportment and impulsive violence is noticed. The patient thus shows symptoms of psychical akinecy and hyperkinecy, too. In encephalitis lethargica a clinical picture may be had which, in extreme cases with stupor, resembles the schizophrene catatonia in a bewildering way. On the other hand a number of disturbances of movement may be seen in catatonia that are analogous in an astounding way to the disturbances of movement in encephalitis lethargica. Gadelius considers that the stupor in affectations in the central ganglions and in the catatonia in schizophreny — though they are not identical either pathologic-anatomically or psycho-pathologically — are similarly *instrumented*. They have a *split mental life* in common *in which psychic, motoric or psycho-motoric functions, directed from the central ganglions are detached from the unity and appear independently.*

Herewith Gadelius comes to hysteria. He questions, first of all, whether the central system of ganglions in certain primitive peoples, as well as in the child, still retains any of its original autonomy. He thinks, in this case, of epidemic forms of mass hysteria with involuntary and choreatic phenomenon of movement that still occur among rather primitive human races and that appeared during the middle-ages in such forms as the Tarantella in Italy, and the St. Veitz' dance in Central Germany. »We here stand before mass phenomena, when primitive horror and extacy like a psychical contaigeon carried away with it thousands and thousands, and these

appearances are certainly more easily understood if they are compared with certain animal mass-phenomena which must be placed in the primitive animals' simple nerv apparatus of the mind.»

He carries the thought further: »If these suppositions contain any truth I dare, finally, question, whether the more sporadic hysteria may not be looked at from the same angle. I do not take the common cases into consideration in which the way of hysterical reaction is founded on a beginning catatonia or other kind of mental disease at an early stage, but I refer to the hysteria in a more genuine meaning, in which *a predisposition to opportune psychosis is connected with the child's less developed structure of mental life and with the mental life of certain persons of a primitive stage of development.* Such an inferiority which may be called a disease must, as well as every other psychical peculiarity, possess an organic fundament and the question is close at hand, whether the subcortical ganglions here, too, retain something of their animal autonomy? Does not the whimsicalness of the hysteric, his impulsive way to follow the inspiration of will, the predominance of affects over reflection and consideration, certain compulsory actions and disordered choreatic movements during the attacks of hysteria, does not all this, as well as the easiness with which certain ideas and complexes influence the vegetative centres and easily suggested symptoms in the body, in the autonomy mentioned, depend upon, and cannot these, certainly primitive qualities in the psychic of the hysterical person be explained by the deficient developement of the inhibiting centres in the lobe of the forehead, which in him and the child and the semi-wild man are unable to restrain the animal mind?»

Summarizing Gadelius one may say that he sees, in the hysterical symptoms, an expression of the independence that the subcortical ganglions attain when the mental life is split by hysteria.

Gadelius' theory can neither be proved nor thrown over. It has, however, a suggestive elegans and seems to have a certain value as a working hypothesis for the psycho-pathologist. When I was attending a number of »shell-shock» cases in the Finnish army, in summer 1941, I noticed that many of the »tremblers» and »the stuporous» reminded me surprisingly of Economo-encephalite patients, and Gadelius' thoughts ran into my mind. A close examination of 20 cases brought out circumstances that may be of some interest.

·*Cases.*

Case 1. R—n, M. 36 years. Smith. Admitted 14. 8. 1941.

Heredity: No psycho-pathological heredity discovered.

Previous mental state: Has visited one physician after the other on account of abdominal troubles which have not been defined. A good worker, says his nerves are strong.

Anamnesis: Some days ago present in concentrated trench-mortar fire. A shell exploded near him. *Lost consciousness,* was taken to the Battalion First Aid Station where he awoke after some hours. *Blood flowed from his nose and mouth, headache, vomiting and general trembling.*

State at admission: Heart, lungs and abdominal organs, nothing noteable.

Mental state: Seems »normal». Afraid to sleep on account of horrible visions in his dreams, jumps at every little sound. Appears exceedingly terrified.

Neurologic symptoms: Posture free. Expression of face rigid with a *suggestion of mask-like face. Right hand shakes* with a frequency that lies on the border between slow tremor and shaking in paralysis agitans. The trembling comes in series with intervals of a few seconds. Stops during sleep, increases when the patient is agitated. No movements in left hand. When the patient walks or runs the trembling is still there, *asynergia in right arm. Synergia of left arm normal.*

Course: When the patient was discharged 10 days later, the symptoms were less pronounced.

Case 2. V-n, K. 38 years. Home stead farmer. Admitted 6. 8. 1941.

Heredity: Father committed *suicide.* A sister »queer».

Previous mental state: Nerves always weak.

Anamnesis: When the patient was on guard a week ago, some Russians approached the line. The patient sank down with fright, felt giddy, began to tremble and was overtaken by complete powerlessness. Was taken to BFAS. He was uneasy, tired, sleepless and »unsteady».

State at admission: Heart, lungs, abdominal organs, n.n.

Psychically the patient seems debile. Conduct pitiable and stupid. Sleep broken by nightmare.

Neurologic symptoms: Posture free. Ordinary expression. *He shakes continuously and with the same frequency as in patients suffering from paralysis agitans.* The shakings stop during sleep but increase when the patient is excited. No shakings in hands, but during walking asynergia in left hand. Synergia of right arm normal.

Course: After one week the patient was discharged and the shakings of the head had disappeared, the synergia had returned, but the psychical weakness was unchanged.

Case 3. K—i, J. 41 years. Farmer. Admitted 25. 7. 1941.

Heredity: No information.

Previous mental state: Nerves always weak. Cried easily.

Anamnesis: Five days ago a mine exploded close to the patient. He

lost consciousness and remembers nothing of what happened. Since then headache, vertigo, visions of terror, fits of crying and shakings.

State at admission: Heart, lungs and abdominal organs, n.n.

Mental state: Uneasy and afraid. Cries when spoken to, does not speak to other patients.

Neurologic symptoms: Walks slowly and retardingly, with a *suggestion of muscle rigidity. Right hand shakes with typical paralysis agitans character.* Left hand normal. Asynergia in right arm during walking but cooperative movements normal in left hand.

Course: The neurologic symptoms decreased gradually and disappeared after two weeks in hospital, then discharged. No fits of crying or visions of terror.

Case 4. J—n, J. 23 years. Farmer's son. Admitted 25. 8. 1941.

Heredity: No information.

Previous mental state: Attended for »weak nerves» in 1939.

Anamnesis: In the morning a shell dropped at a distance of 4 metres from him. Remembers nothing later. *Flow of blood* from *nose and mouth.*

State at admission: Heart, lungs, abdominal organs, n.n.

Mental state: Gives the impression of a bad psycho-neurotic. Sleepless, dreams of terror.

Neurologic symptoms: Posture and gait ordinary. *In right hand shakings of paralysis agitans type* which increases when irritated but lacking during sleep. Left hand and cooperative movements ordinary.

Course: Shakings stopped after one week.

Case 5. K—o, 0. 26 years. Labourer. Admitted 6. 8. 1941.

Heredity: A brother insane.

Previous mental state: Could never stand adversities, weak nerves and cried easily.

Anamnesis: Five days ago in concentrated trench-mortar fire, began to shake and cry and was taken to the Field Hospital in a muddled state. Since then shakings, headache, sleepless, vertigo, nervous and weak.

State at admission: Heart, lungs and abdominal organs, n. n.

Mental state: Somewhat absent-minded. Speaks in a low voice and softly, often to himself. Bursts out cyring suddenly.

Neurologic symptoms: Posture fairly free. Expression rigid but no »masklike face». Gait free, walks as if absent-minded with his hands on his back like a philosopher in deep thought. When he lies down or sits the right leg *shakes with a frequency of 160 per minute.* Left leg still. Cooperative movements in arms normal. Regular *tics in left side of face. The head shakes in a complicated rythm of motion* — he turns it slowly from side to side, at the same time he bends it backwards and swings it sideways with lesser amplitude (like a screenwiper that is seen in winter in shopwindows to keep the windowpane free from ice.)

Course: The leg-shakings disappeared in three weeks. Psychically more free, worked in the joiner's workshop at the hospital but with a very poor result. The shakings of the head did not change, however, during the whole time of observation which comprized more than half a year.

Case 6. N—n, U. 20 years. Homestead farmer. Admitted 28. 7. 1941.
Heredity: No information.

Previous mental state: Weak nerves all his life.

Anamnesis: Dropped down during an attack yesterday, began to tremble and cry. Was sent away as his right hand shook so that he could not carry his gun. Had not slept, had had visions of terror.

State at admission: Heart, lungs and abdominal organs, n.n.

Neurologic symptoms: Stands slightly bent forward with both arms sligthly flectered (In passive movements a tough resistance, rigiditas cerea.) In right *hand shakings that in frequency and movement resemble that of paralysis agitans. Left hand still. Walks stiffly, groping toughly like an Economo-patient. No synergia in arms nor trunk. Cannot be persuaded to run.*

Mental state: Dreams of terror. Feels he must go to attack all the time. Speaks very little. Lies curled up in bed. Fits of crying.

Course: Stiffness in posture and rigidity decreased within a week but remained to some degree during the whole time of observation. Paralysis agitans in the hand remained unchanged. At an alert 3 weeks after admission he had a fit of violence, fought wildly and after having been over-powered he lay in bed for three days quite stiffly, cataton. (Bewegungs-sturm and Totstellereflex). His condition improved gradually but still two months after admission the shakings of the hand were unchanged. He got more and more depressed and was transferred to the Mental Ward.

Case 7. L—n, E. 20 years. Chauffeur. Admitted 4. 9. 1941.
Heredity: No psycho-pathological inheritance found.

Previous mental state: Says that he has been »quite ordinary».

Anamnesis: Present in trench-mortar concentration 3 days go and became unconscious. Carried on until last night when present in a second trench-mortar concentration he lost consciousness again.

State at admission: Heart, lungs and abdominal organs, n.n.

Mental state: Lies curled up on his side in bed, holding his hands as if shooting with a machine-gun. Hands shake violently. Mumbles »pam, pam, pam» to himself. Does not react when spoken to. Will not eat but drinks when the cup is put to his lips. After two days he becomes conscious, the »shooting» stops, and he is able to give anamnestic replies.

Neurologic symptoms: (4 days after admission). *A suggestion of general rigidity* and *mask-like face.* When looking sideways he does not turn his head. Walks slightly bent forward, unsteadily, staggers occasionally. *In right hand shakings of typical paralysis agitans appearance* combined with supination and pronation movements. *Arm slightly flectered in elbow joint.* Left hand still. *During walking no synergia in arms nor in body.*

Course: Condition gradually improved. Gait more firm, but a certain rigidity still there. Paralysis agitans remained unchanged during 2 months of observation. Synergia returned to left arm but not to right arm. No synergia noticed either during running.

Case 8. P—a, 0. 30 years. Labourer. Admitted 5. 8. 1941.
Heredity: No information.

Previous mental state: Has always been considered »nervy».

Anamnesis: 4 days ago a shell exploded close to him. Does not recollect the incident.

State at admission: Heart shows signs of myoaffectation, lungs and abdominal organs, n.n.

Mental state: Clear in his head, but gives the impression of being intoxicated.

Neurologic symptoms: Gait slightly tottering as if intoxicated, expression dull, but no mask-like face. *Strong flow of saliva. In right hand typical paralysis agitansshakings. During walking tremor in left hand. No cooperative movements in either arm.*

Course: The symptoms disappeared quickly. In 10 days the shakings disappeared and synergia returned.

Case 9. R—n, T. 23 years. Glassblower. Admitted 5. 8. 1941.

Heredity: A sister feeble-minded.

Previous mental state: Weak nerves since childhood. Nervous collapse at the front in the war of 1939—40.

Anamnesis: Lost consciousness 3 days ago during a trench-mortar concentration. Since then headache, vertigo, sleeplessness, dreams of terror, shakings.

State at admission: Heart, lungs and abdominal organs, n.n.

Mental state: Appears frightened, but quite clear in his mind.

Neurologic symptoms: Staring mimicless masklike face. During rest paralysis agitans shakings in right hand. During walking the shakings increase and jerky, regular *choreatic twistings of the upper-arm occur as well.* Asynergia in right arm, in left arm normal movements.

Course: The symptoms disappeared in one week.

Case 10. A—n, A. 27 years. Farmer. Admitted 14. 8. 1941.

Heredity: No information.

Previous mental state: Nerves always weak.

Anamnesis: The day before yesterday, the patient's second day at the front. 4 men were killed close to him and since then he does not remember anything before he became conscious on board the evacuation ship.

State at admission: Heart, lungs and abdominal organs, n.n.

Mental state: not mentally clear but replies to questions. Looks around terrified and mumbles »there are boys here, our own boys». Does not talk otherwise.

Neurologic symptoms: Mimicry lively, no mask-like face. *In the right hand tremor of about* 300 per min. frequency. *Both arms slightly abduccerated in shoulder joint during walking and asynergia.*

Course: In a few days the patient was mentally clear. Dreams of terror tortured him. After 4 days synergia in left arm returned. Trembling, rigidity and synergia in right arm remained unchanged during observation of 4 months. The patient remained incapable of work, complained of not being able to concentrate, frightened, vertigo, headache and »awkwardness and strange feeling in right hand.»

Case 11. L—a, A. 30 years. Farmer. Admitted 6. 8. 1941.

Heredity: Father habitual drunkard.

Previous mental state: During the war 1939—40 m—g man at the front, »where *his nerves were destroyed*».

Anamnesis: Lost consciousness this morning during a trench-mortar concentration. Awoke at BFAS, vertigo, sounds in ears, and did not hear very well. Does not remember much.

State at admission: Heart, lungs and abdominal organs, n.n.

Mental state: Conduct somewhat hysterically theatrical. Says he is deaf but reacts when his name is whispered. Dreams of terror.

Neurologic symptoms: Posture and mimicry ordinary. *In right hand shakings of typical paralysis agitans character.* They increase if patient is excited and disappear almost completely during rest. *During walking the arm is slightly abducerated and lacks synergia.*

Course: During the time of observation (one month) the patient's condition grew worse. Paralysis agitans in his hand increased and a state of highly querulant hysteria developed.

Case 12. S—g, T. 23 years. Labourer. Admitted 4. 9. 1941.

Heredity: No information.

Previous mental state: Says he has been just an ordinary man.

Anamnesis: At the fireing-line since end of June. Got more and more »nervous» during artillery fire. 4 days ago, when a shell exploded close to patient, he collapsed and began to cry and shake.

State at admission: Heart, lungs and abdominal organs n.n.

Mental state: Lies an cries, complains of feeling agony and having dreams of terror. Sleepless.

Neurologic symptoms: Rigid mimicry and rather pronounced mask-like face. Walks slightly bent forward, stiffly, lacking synergia as an Economo-patient. In right hand paralysis agitans shakings of medium frequency. Arm slightly abducerated in shoulder joint and rotating outwards. Left hand still.

Course: The general rigidity disappeared in a few days. The shakings in right hand remained for 3 weeks but in a lesser degree. Synergia in left arm returned but not in the right one.

Case 13. L—n, J. 30 years. Farmer. Admitted 4. 9. 1941.

Heredity: No nervous diseases infamily.

Previous mental state: Says he has been just an ordinary man.

Anamnesis: Has slept only a couple of hours every night for one whole month. »Felt worn out» and when he was to bandage a wounded soldier during a trench-morter concentration, everything went black and he did not regain consciousness until he was in the War Hospital.

State at admission: Heart, lungs and abdominal organs, n.n

Mental state: Not clear the first day, cannot account for anything. Next day clear, and describes things correctly as he remembers them. He cannot understand »what came over him».

Neurologic symptoms: General rigidity. Walks with a forward bend, with short steps (march a petit pas) *and with synergia lacking in trunk or arms. In fingers of left hand pill-rolling movements of the same kind as in paralysis agitans.* Mimicry dull but no masklike face. *Complains of dryness in mouth.*

Course: General rigidity disappeared in a week. Shakings and asyner-

gia in left hand present still one week and then the patient was free from neurologic symptoms.

Case 14. L—a, V. 28 years. Farmer. Admitted 28. 7. 1941.

Heredity: Father suffered from severe fits of depression.

Previous mental state: Always irritable and nervous about little things.

Anamnesis: Yesterday morning a shell exploded in his vicinity. Remembers nothing until he woke up at BFAS.

State at admission: Heat, lungs and abdominal organs, n.n.

Mental state: Complains of agony and fear. Quite clear in his mind.

Neurologic symptoms: Gives a definite impression of an encephalitis lethargica patient, with pronounced mask-like face and hypersecretion of tallow (»Salbengesicht»). *Walks very stiffly, slightly bent forward, no synergia in trunk, arms or head. Bursts out crying. In right hand typical paralysis agitans shakings. Retropulsion tests positive* (continues to walk backwards when pushed backwards).

Course: Within 10 days condition improved in that the general rigidity disappeared. Shakings in the hand remained 2 more weeks and still 6 weeks after admission synergia in the right arm less than in the left one.

Case 15. K—a, T. 39 years. Taylor. Admitted 25. 8. 1941.

Heredity: No information.

Previous mental state: Had a nervous collapse during the war 1939—40 after which his nerves had been weak and his right hand was inclined to shake.

Anamnesis: 10 days ago he became muddled during a trench-mortar concentration and was transported to BFAS. Has no recollection of what happened. Since then sleepless, dreams of terror and shakings in right hand.

State at admission: Heart, lungs and abdominal organs, n.n.

Mental state: Gives the impression of an »inferior neurotic». Clear in his mind.

Neurologic symptoms: Posture and mimicry ordinary. *In right hand typical paralysis agitans shakings, asynergia during walking.* Left hand still, ordinary cooperative movements.

Course: The shakings disappeared in a week but returned at the slightest physical exitement. Synergia returned.

Case 16. N—n, E. 33 years. Farmer. Admitted 26. 7. 1941.

Heredity: No information.

Previous mental state: No information.

Anamnesis: Three weeks ago the patient was *showered with earth and stones* in an artillery-fire concentration, he became unconscious and had a small wound from a splinter. Since then severe headache, sleepless, and his right hand trembles to such a degree that he cannot hold his gun. »Sent away on that account».

State at admission: Heart, lungs, abdominal organs, n.n.

Mental state: Clear in his mind, complains constantly of his head aching, asks for headache powders all the time.

Neurologic symptoms: A suggestion of mask-like face and a certain general rigidity. In right arm typical paralysis agitans shakings. During walking asynergia in this arm. Left arm ordinary.

Course: The shakings disappeared in two weeks and the synergia returned. The headache persisted during the whole time of observation (one month) and the patient became more and more neurotic.

Case 17. T—n, T. 36 years. Labourer. Admitted 27. 7. 1941.

Heredity: A sister insane.

Previous mental state: 5 years ago in mental hospital.

Anamnesis: Sleepless during 2 weeks. Ran away from the firing-line yesterday and was taken to BFAS.

State at admission: Heart, lungs and abdominal organs, n.n.

Mental state: Dull-witted, a slovenly type of psychopat.

Neurologic symptoms: Posture and mimicry normal. *In right hand quick coarse tremor. Nodding, fine beating shaking of head. During walking asynergia in right arm.* The left one normal.

Course: Shakings stopped within a month and cooperative movements of the right arm returned.

Case 18. Y—n, V. 33 years. Homestead farmer. Admitted 14. 8. 1940.

Heredity: No information.

Previous mental state: Has consulted physician on account of his weak nerves.

Anamnesis: The day before yesterday he lost consciousness during a trench-mortar concentration. No recollections. Since then sleepless, tremblings, vertigo, headache and nausea.

State at admission: Heart, lungs and abdominal organs, n.n.

Mental state: Appears to be debile.

Neurologic symptoms: A suggestion of mask-like face. Posture free *In. right hand jerking coarse tremor. During walking asynergia in right arm but left arm normal.*

Course: The patient was discharged the same day.

Case 19. N—n, O. 23 years. Farmer's son. Admitted 9. 8. 1941.

Heredity: No information.

Previous mental state: No information.

Anamnesis: 3 days ago the patient began to throw imaginary hand-grenades at imaginary people in the woods and was taken to BFAS in a muddle state.

State at admission: Heart, lungs and abdominal organs, n.n.

Mental state: Clear in his mind, frightened, dreams of terror, complains of vertigo and headache.

Neurolotic symptoms: When the patient is exited, *coarse tremor appears in the right hand.* During walking asynergia in this hand. Left arm normal.

Course: The patient was discharged after 5 days. No changes.

Case 20. J—ä, A. 37 years. Home stead farmer. Admitted 5. 8. 1941.

Heredity: No nervous diseases in family.

Previous mental state: Says his nerves have always been good.

Anamnesis: 3 days ago he lost consciousness during artilleryfire concentration and did not regain consciousness until at BFAS. Since then headache, vertigo, sounds in ears, vomiting and dreams of terror.

State at admission: Heart, lungs and abdominal organs, n.n.

Mental state: Conduct free and normal.

Neurologic symptoms: Mimic somewhat rigid but no typical mask-like face. Posture normal. *Typical paralysis agitans shakings in right arm which is slightly abducerated in shoulder joint during walking, and lacks synergia.* Left arm normal. During running the shakings increase but cooperative movements do not occur.

Course: The shakings, during rest, disappeared in a week, but returned still after one month if the patient was excited or worked hard. He still complained of headache, uneasy sleep and nervousness. Further reports lacking.

Summary of Cases.

The 20 cases which have been reported are such that could be termed »tremblers» directly on superficial examination. Though time was short very careful observations were made. Conditions were such, however, that it was impossible to make a thorough anamnesis, especially in regard to heredity and previous mental state. Such schematized expressions as »bad nerves» and reports of a single psycho-pathological case in the family had to suffice. It is evident that there must have been more than 20 cases of the kind described here among the total number of 162 cases.

Observations of interest may be summarized in the following points.

1. Hereditary psycho-pathology or signs of mental inferiority were found in 14 cases.

2. 4 patients had had a nervous collapse during the war in 1939—40.

3. The reaction was similar in all patients. In connection with a psychic trauma, causing terror of a varied degree, such as an explosion of shells in the vicinity, sudden attacks, artillery concentrations etc., the patients had fallen into a state of *obfuscation* which in the greater number of them developed into complete *unconsciousness* and *amnesia*. We must notice that a commotio cerebri might have been possible in 3 cases (1, 4 and 16), in 6 cases (2, 6, 10, 13, 17, 19) the reaction was definitely not caused by a preceeding scull trauma. In all other cases (3, 4, 5, 7, 8, 11, 12, 14, 18, 20) the collapse occurred during trench-mortar fire and the effect of airpressure must be taken into consideration.

4. After awaking from obfuscation the patients suffered partly from general symptoms such as headache, vertigo, nausea, sleeplessness, nightmares or of neurasthenic symptoms, and partly from tremblings and rigidity.

5. *These isolated symptoms were very characteristic.*

In very pronounced cases the patient gave an absolute impression of an Economo postencephalitic patient with a rigid mask like face, »Salbengesicht», a general rigidity, asynergia during walking, and shakings in arms or hands of the same kind as in lethargic encephalitis, paralysis agitans or Parkinsonism. In the less pronounced cases some of the symptoms were not present. 7 patients suffered from general rigidity (3, 6, 7, 12, 13, 14, 16). 5 of the last mentioned showed stiffness in mimicry or mask like face and 5 shakings and lack of cooperative movements in the right arm. 3 patients (9, 18, 20) rigidity of mimicry combined with shakings in the right arm and asynergia. Cases 2, 5 and 17 showed shakings of the head. Case 5 suffered from shakings of the leg and tics. Case 2 lacked cooperative movements in the left arm. Case 17 combined shaking of the head with shakings and asynergia in the right arm. In 5 cases (4, 8, 10, 11, 15) shakings in the right arm only occurred and cooperative movements were lacking in the arm. In 1 case only, case 13, there were shakings and asynergia in the left arm. Case 8 had a flow of saliva and in case 9 choreatic movements in the right arm occurred.

6. The course was favourable in most of the cases as the neurolitic symptoms disappeared within a few weeks or a month. Shakings were present for 6 weeks to half a year in 5 cases only.

Discussion.

20 reactive mental cases, in which there were pallidostriatic symptoms, have been reported under the heading »Cases». The first question to be put now is whether the cases may be called war hysteria.

The actual causes have been terror and a desire to get away from the hellishness of the fireing line. In many of the patients a sign of constitutional psychic inferiority was noticed, a sign that

shows that they were »subsolid». The overpowering psychic exertions were too much for them. As a last way out the mechanism of hysteria, the splitting of mental life, was set free. The connection between the various components of the mind was loosened. A chance of a conscious suppression, an obfuscation and an unconsciousness, and of a rise of isolated symptoms was created. By these means the mental disease was attained, a disease with a purpose of delivering the patients from the horror of the war. The reaction was »opportume», it was an »escape into sickness», »an illness, the symptoms of which have been created by the desire to demonstrate these symptoms to the surroundings».

We must, however, discuss, whether a scull trauma may play a rôle. In three cases the possible occurrence of a commotio cerebri could not be excluded, in the other cases there was certainly no scull trauma, i.e. if air pressure by an explosion of shells is not taken into consideration. Such a possibility occurred in 11 cases. The cases, where no outside influence has, with certainty, affected the brain, are, however, similar to the other cases, and the three cases that bled from nose and mouth do not either offer any peculiarities. In such circumstances it does not seem possible that external violence could have influenced the shaping of the symptoms.

The isolated neurologic symptoms where, in the pronounced cases, a general rigidity with mask-like face and »Salbengesicht», such as it appears in encephalitis lethargica, in other cases shakings and tremor, as in paralysis agitans, asynergia, tics, choreatic movements and disturbances in the secretion of saliva.

Muscle rigidity and poorness in the motorical capacity belong to globus pallidus. Lack of cooperative movements in the arms is considered to be an early symptom. Substantia nigra generally collaborates in very severe rigidity. Striatum is the site of chorea and atetos but thalamus is said to collaborate as well. Tremor and regular shakings belong to nucleus ruber tegmenti, but tics and local spasms in the muscles are considered »striäre Enthemmungsphenomene circumscripter Lokalisation». Hypothalmatic symptoms, such as disturbances in the secretion of tallow and saliva, may be mentioned.

When such symptoms arise in encephalitis lethargica or in paralysis agitans we admit, without objections, that they are paleostria-

tic, as we know that they are founded on pathologic-anatomical changes verifiable microscopically. The position is different in the cases that I have desscribed above. It is impossible to prove and, besides, it is hardly probable that there were conceivable anatomical changes in the central ganglions. Are the symptoms in these cases pallidostriatic? Are they caused by the subcortical canglions?

When the patients presented themselves their symptoms were so evidently classical that an association with Economo-encephalite appeared at once. Any doubts of the shakings, the choreatic movements, tremor, tics, etc. being simulated or suggestive, i.e. having been placed on a higher, more conscious level of will, were dispersed by the severely split mental state of obfuscation in the patients. Secondly, the symptoms that were noticed in all patients but one, i.e. *asynergia during walking,* in both arms or in one of them, is a strong evidence of the paleostriatic instrumentation. Finally, it seems rather strange to deny, but there is no doubt about it, that symptoms that have been localized in the central ganglions are not directed from these centres if they appear with no evident organic foundation.

. We have thus the right to consider these symptoms paleostriatic but, lacking a hold on an organic foundation, we call them functional. We mean by this, as so often in human pathology, that the symptoms have arisen on account of activity in the organ in question, though no diseased changes in the cells that may have caused this function have been detected. Parallels to these »functional» disturbances in the secretorial apparatus may be drawn up, for instance such as the clinical picture of Morbus Simmond »in nervous emaciation» or, psychogenetically predisposed tyreotoxicoses. Characteristic traits of the functional symptoms seem to be that the organ that is finally responsible for the shaping of the symptoms, is not the site of any evident diseased process but its normal function has been changed by the influence of an other instance. In the fundamentally organic Morbus Simmond the hypophysic is the site of primary diseased changes in the cells of one kind or another, in the »nervous form» the cells of the hypophysis function in the same diseased way on account of lacking collaboration with superior controlling centres of the brain.

In this way the paleostriatic symptoms in my patients may be understood. They are not fundamentally organic changes of the

cells in the subcortical ganglions but are accounted for by a changed function in them which again is caused by a superior centre.

But how has this change arisen?

Gadelius's idea was that the hysterical reaction consists of a splitting of the mental life whereby lower impulses, affectations, actions by power of will and instinct, localized in the central ganglions, become independent. The »animal mind», contained in the subcortical ganglions, are withdrawn from the governing and inhibiting control of the cerebral cortex. Hysteria is the primitive autonomy of mental life, localized in the subcortical ganglions.

If we follow Gadelius it seems convincingly logical that symptoms in the motorical central ganglion should appear as well in the hysterical reaction. If we wish to believe that the psychic functions of the central ganglions become independent we may surmise that their motoric functions may withdraw from the control of superior parts of the brain. *The paleostriatic symptoms of hysteria would thus be an expression of a functional disturbance in the subcortical ganglions accounted for by the control and reciprocity with other parts of the brain being withdrawn.*

We should, however, underline the fact that paleostriatic symptoms in war hysteria seem to be rather common but on no account obligatory. The clinical picture is often mastered by psychic symptoms or by hysterical paralysis, anesthesies, deafness etc. This is a logical result of the mechanism of the hysterical reaction: When the mental life is split any part may attain the independence that leads to the symptoms becoming manifest. We must, if we wish to follow this reasoning, avoid every analysis of details and systematic arrangement. These thoughts do not represent a systematic localization of physical and motorical functions in any defineable parts of the brain, as Gadelius particularly points out. The complicated structure of mental life is the result of a new construction gradually being erected during the time of development. Its various phases correspond with the various phases of the development of the brain. When something new has been added to this structure the old parts have not been demolished but have been taken up into the new sections as a unity. When the mental life is split by psychical diseases and the unity falls to pieces the psychic and motorical functions, that phylogenetically are as old as certain parts of the brain, may establish an autonomy in its parts of the

brain. But this must not be taken in a figurative sense. The various components of the mental life cannot be localized with any certainty. A psychical or psycho-motorical occurrence may take place in different parts of the brain and is dependent of the joint efforts of the cooperating parts of the brain. Its localization of the moment will depend upon what other psychical occurrence it is connected with, or from what psychical point of view it is regarded.

In view of these reservations the peculiarities of war hysteria seem to offer two aspects. *On the one hand occurrences of pallidostriatic symptoms in hysteria may most easily and most elegantly be explained by the aid of Gadelius's theory. On the other hand the symptoms as such seem to represent an argument on the reliability of Gadelius's reasoning.*

There is reason to point out as well hat Gadelius's theory signifies that pallidostriatic symptoms may be expected especially in reactions caused by fright. The motorical phenomena, described above, form the basis of fragments or rudiments of the primitive reaction of fright »Bewegungssturm» and »Totstelle-reflex». Hyperkinetic shakings, trembling and choreatic movements, and tics correspond with the motorical storm while the muscle rigidity and the motorical poorness correspond with the imitation of death. Case 6 was interesting in this respect — he had an attack of violency during an alert, followed by 3 days of catatonic stupor.

Summary.

1. A report on Gadelius's theory on the mechanism of hysteria. The issue of the theory is that the symptoms are an expression of the independence that the subcortical ganglions attain when the mental life is split by hysteria.

2. A report on 20 cases of war hysteria in which pallidostriatic symptoms appeared in the form of muscle rigidity, motorical poorness, stiffness of mimicry, shakings, tremor, choreatic movements, tics, and flow of saliva.

3. In accordance with Gadelius's theory these symptoms are to be apprehended as an expression of functional disturbances in the subcortical ganglions which have arisen when the mental life has been split by the hysterical reaction, and reciprocity of the various parts of the brain have been disturbed.

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The Value of Ascorbic Acid as a Prophylactic against »Common Colds».[1]

By

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(Submitted for publication August 25, 1944).

Introduction.

The so-called catarrhal infections are, from a medical view-
point, generally not of a serious nature, even though lengthy and
serious diseases may ensue in a number of cases. However, the
great frequency of these infections entails the loss, wholly or in
part, of a considerable number of working-days within schools,
at places of work, and in military camps. Such infections are con-
sequently very important from social and military viewpoints.

A not uncommon opinion nowadays is that the increased fre-
quency of catarrhal complaints during late winter and spring is
associated with an increased receptivity to infection, due to hypo-
vitaminosis and certain other nutritional derangements. Expe-
riments on animals and clinical observations bear out the wide-
spread view that Vitamin C possesses bactericid and some kind
of immunobiological properties, and can therefore be regarded as

an anti-infectious vitamin. Other authors do not think there is sufficient support for this view; the increased receptivity to infections attendant on clearly manifested Vitamin C deficiency is probably not caused by the vitamin itself, but by the decline in the body's powers of resistance, a state which characterizes nutritional derangements in general. The problem is not easy to solve, since in practice an inferior diet is, as a rule, inadequate in more than one respect, even if a deficit of one constituent may dominate. For the extensive literature on the subject, we refer to text-books and general articles (Stepp, Kühman and Schroeder, 1939; Bichnell and Prescott, 1942; Seidenstücher, 1943; and others).

The extent to which a mild C hypovitaminosis (or, more correctly, perhaps, mixed forms of hypovitaminosis, where the lack of Vitamin C dominates) occurs in Sweden has not been sufficiently clarified, no doubt due to the difficulty of diagnosing with certainty an incipient lack of this kind. Investigations have yielded divergent results, which are difficult to interpret; in most cases the materials were small, the control material inadequate, and the statistical treatment unsatisfactorily carried out.

At the time our investigation was planned (1940), this ambiguous situation was being more and more exploited commercially. The advertisements for medicines and patent foods not infrequently cited publications where more or less over-hasty conclusions had been drawn.

We therefore thought ourselves justified in examining afresh the question as to the value of ascorbic acid as prophylactic against catarrhal infections; in so doing we have endeavoured to obtain a sufficiently large material and satisfactory control-material, and sought to apply suitable statistical methods.

Our investigations were completed in 1940 and published in a preliminary form in 1942; since this time, others dealing with the same questions have appeared. Most of these have been made without controls and on too mixed a material for the results to have any crucial value. The following works in particular should be of interest to our approach.

Demole (1943) gives a general survey of the C hypovitaminosis observed in different armies, and suggests that the deficiency be met by daily administration of 25 mg of synthetic ascorbic acid per person during the winter and spring months. Data collected by

Roff and Glazebrook (1939) from the English Navy shows a C deficiency of up to 4 g. Reports as to the Vitamin C standard in the German army show there to be a deficiency varying between 1.1—3.6 g (Stutz and Reil, 1938; Kramer, 1937; Stutz and Weispfenning, 1939; Kraft, 1940). According to an investigation by Sobecki (1939) the C deficiency for the Polish army amounts to about 2.0 g. As far as we have been able to discover, no controls were used in these investigations to establish whether the Vitamin C deficit proved detrimental to the persons in question. Obviously, it is this question which is of crucial importance.

Bergquist (1940) found reason to suspect that a combination of ascorbic acid and quinine prevents catarrhal diseases. Hamne (1941) disagreed with this and Bergquist (1943) later on took up the question for fresh testing. This time his material comprised 855 males aged 20—60 years, employed at a Swedish ironwork. Of these, 136 were controled, and received tablets without ascorbic acid or quinine. 141 persons received a daily dose of 9 cg quinine sulphate, 128 received 9 cg ascorbic acid, and the remaining 146 workmen were given 9 cg quinine sulphate + 9 cg ascorbic acid, all in tablets. The investigation proceeded for 3 months under as similar experimental conditions as possible for the different groups, and the results were treated statistically at the State Institute for Human Genetics and Race Biology. The investigation showed that, neither with nor without quinine, does Vitamin C have any prophylactic effect in catarrhal complaints.

As against this result there is an investigation carried out in Holland by Oskam (1942) on 392 factory-workers. Oskam used exactly the same division of the material into 4 groups, and the same dosage of ascorbic acid and quinine, as did Bergquist.

A statistical treatment by us of the figures, Oskam submitted for the number of cases of disease within each group, shows that only the combination 'Vitamin C + Quinine' had a statistically significant difference. On the other hand, the effect on the number of working-days lost was statistically significant within all 3 groups receiving respectively ascorbic acid, quinine and ascorbic acid + quinine, when compared with the control-group. The divergent results thus obtained by Bergquist and Oskam might perhaps be explained by the different standards of nutrition probably existing in Sweden and Holland during the war years.

Hjärne (1942) investigated the concentration of Vitamin C in the blood plasma of Swedish schoolchildren aged 7—14 years. No difference could be found between boys and girls, or between the different ages. The highest values were obtained in October, and the lowest in April—May. There was no connection between the number of cases of disease and days of absence, and the vitamin concentration.

Hammar and Schröderheim (1942) investigated 1000 elementary-school children for the effect of dog-rose hip extract on catarrhal infections. During the period February—June 1941, 500 children were given hip extract in apple-juice (corresponding to 50 mg of ascorbic acid per day), while the remaining 500 only received apple-juice. No difference could be observed between the two groups as regards the frequency, intensity or length of common colds.

Korbsch (1938) claimed to have obtained good results from treating colds with large doses of ascorbic acid (1 g daily); however, he got just the same result from the control group, which were given inactive tablets containing citric acid. Glazebrook and Thomson (1942) were similarly unable to observe any decrease in the intensity or course of common colds after the administration of Vitamin C.

Comprehensive investigations were carried out in Germany during the winters of 1941 and 1942, to discover the effect of extra administration of ascorbic acid (Ertel, 1941, 1942). The investigation comprised 3—4 million people (expectant and nursing mothers, infants and schoolchildren) whose diet had been supplemented by ascorbic acid for more than 5 months. The results showed increased powers of resistance to infection in the infants; the mothers showed less sickliness, better appetite and more milk when nursing, and the schoolchildren showed improved output of work, and less colds. Unfortunately, it has nevertheless been impossible to carry out the investigation satisfactorily, i.e. with control groups of persons not receiving extra ascorbic acid. The results are based mainly on the subjective judgments of the test subjects, and the conclusions are also of a subjective nature.

Plan for the investigation.

In the first place, a Vitamin C deficiency is to be expected in Sweden during the late winter and spring. Further, the popula-

tion in the most northerly parts ought to be more exposed to such a deficiency than the population in the rest of Sweden. For this reason our investigations were arranged to cover the period February-May 1941, and the material taken was an infantry regiment stationed at an isolated region in northernmost Sweden, some Swedish miles south of the Arctic Circle.

The regiment went to the camp in question round about 15th January. The material comprised about 2,500 men, most of whom came from upper Norrland. The investigation did not include officers, non-commissioned officers, or persons who had left the camp before March 24 for reasons other than illness.

The diet was the regular one for troups stationed in Northern Sweden, but also including 4 g of skorbon per week. Two weeks before the experiments began, the skorbon and food containing hip was left out, and all the skorbon on the premises withdrawn. The provisions sold at the canteen were placed under control, ensuring that no Vitamin C worth mentioning was supplied through this channel.

As the primary aim of our investigation was to establish the value of ascorbic acid as prophylactic against colds, it may well have been practical to have rendered the normal diet poor in Vitamin C, thus producing a considerable difference in the Vitamin C standard between the control group and the group receiving an extra supply of ascorbic acid. In order to obtain an answer to the vexed question as to whether so-called normal military fare in Sweden is sufficient to keep the troup at a desirable Vitamin C standard, or whether the addition of extra ascorbic acid might decrease the frequency of colds while raising the general condition otherwise, we nevertheless thought it wisest to alter the fare of that time only as regards the remedy skorbon and hip. It would seem from a study of the feeding list (Suppl. 1—4) as if the content of Vitamin A is relatively low. A year later, Engel, Granström, Lindgren and Nordlander (1942) made investigations comparing the Vitamin A standard of soldiers with practically the same fare as the one we used (1700—1800 I.U. Vitamin A), with that of soldiers receiving in addition an extra supply of 3,700 I.U. Vitamin A; the results obtained showed both groups to present normal serum values for Vitamin A and for B carotins and that both the groups had normal ocular perceptivity, both at the beginning of the

test period and at its termination, 24 days later. Thus, the Vitamin A standard maintained by the fare used by us can be denoted normal.

The administration of ascorbic acid was begun on March 3, and continued to May 31 inclusive. On account of the special circumstances, we were in a position to obtain control material which is completely suitable from a statistical viewpoint. All soldiers with odd identity numbers were given tablets containing ascorbic acid, and soldiers with even identity numbers were given control tablets, to which a suitable amount of citric acid had been added, to disguise any difference in taste. The tablets were kept in bottles with yellow and blue labels respectively, and their composition was kept secret both from doctors and soldiers. The tablets were dispensed at the first meal of the day, and special steps were taken to see that they were consumed there and then, and did not go to the wrong person. The soldiers were told what the investigation was for, and were requested not to eat any other food or other medicines during the time of observation than what was provided in the camp. The ascorbic group, who were put on 'yellow' tablets, received 200 mg of ascorbic acid daily during the first 24 days, and 50 g during the whole period of observation subsequently. The control material received a corresponding number of citric acid tablets.

A registration card was drawn up for every soldier who fell ill; on this, necessary data as to the disease were entered (see below).

Ascorbic acid titrations with loading tests were made according to a modification of the Tillman test. In addition, capillary resistance tests were carried out according to Dif's (1940) modification of Göthlin's procedure, which proved most suitable for our working conditions.

We should have liked to have obtained a more exact gauge of the Vitamin C standard by more thorough means, e.g. ascorbic acid titrations on blood, but the military field conditions made such plans completely unfeasible. The results we obtained nevertheless give relative values for a comparison between the 'control' and the 'vitamin' groups, and these values seem to bear out the conclusions we have drawn.

Professor G. Westin has been good enough to make a histopathological investigation of teeth extracted from this soldier mate-

rial. His material is too small to allow of definite conclusions, but it nevertheless seems as though this method were not fitted for assessing the Vitamin C standard in investigations of the kind in question. The histo-pathological diagnoses did not agree in a number of cases with the real character of the individuals — we have therefore considered it unnecessary to publish the data here.

Results of the investigation.

a) Ascorbic acid titrations.

After 23 days, when the 'yellow' soldiers had received a total of 4,600 mg of ascorbic acid, the titrations showed a mean reduction value for urine of on fasting 3.5 ± 0.87, and one of 13.4 ± 2.4 two hours later, after a further 200 mg. The difference was thus 9.9 ± 2.6, and may be denoted statistically significant. The corresponding values for the controls were 1.1 ± 0.13 and 1.1 ± 0.12. There is also a statistically probable difference between the fasting values for 'yellow' and 'blue' subjects (i.e. 2.4 ± 0.89).

In so far as ascorbic acid titrations of urine can be assumed to constitute a gauge of the Vitamin C standard, we were thus able to establish a material difference in these standards between the ascorbic acid group and the control group. According to the current opinion, the controls can probably be presumed to have been suffering from a considerable Vitamin C deficit at the time of the investigation.

Despite precautions, there were periods after April 6th when several companies, or some proportion thereof, in certain camps did not always take the tablets regularly.

In the treatment of the material, therefore, we divided it up into two groups: Group I, where, as far as we could ascertain from careful checking, the soldiers had taken the tablets regularly the whole time, and Group II, where most of the soldiers had in all probability taken the tablets for the greater part of the observation period, but only *regularly* during the time 3/3—6/4. However, the material in Group I was sufficient by itself to yield statistically significant results.

At the end of the test period ascorbic acid titrations were made with loading tests. These latter were begun on May 21 with 300 mg of ascorbic acid daily. On May 26, the difference between the

fasting values and the reduction values two hours after taking the tablets was, for the 'yellow' soldiers, probable and, on May 30, it was significant (Difference: 12.6±2.8). The corresponding difference for the 'blue' controls did not show even a tendency to become probable (Difference: 1.5±1.3).

Summing up, then, we can say that, in so far as one can judge from ascorbic acid titrations, there was a significant difference as regards the Vitamin C standard, both during the first part of the observation time and at its termination.

b) Capillary resistance tests.

The capillary resistance tests were carried out at the end of the observation period on 127 'yellow' subjects and 124 'blue' controls. The average number of petechiae were 4 for the former, and 6.2 for the latter, with a statistically probable difference. The difference is slight, however. The results are outlined in diagram 1. Only 5 men had more than 20 petechiae, namely 2 'yellow' sub-
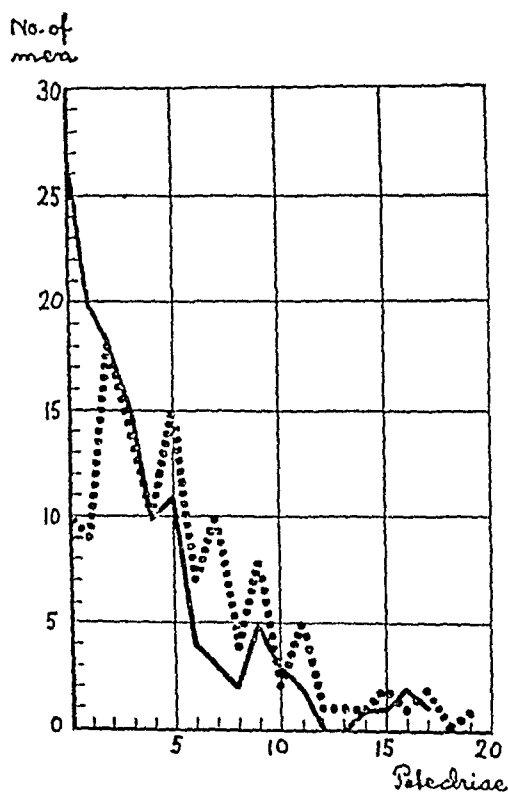
Diagram 1.   Distribution of number of petechiae at capillary resistance tests on 127 men who got ascorbin acid (whole line) and 124 men who did not get ascorbin acid (pointed line).

Table 1.

Registered cases of disease.

	Group I		Group II	
	Ascorbic acid cases	Control cases	Ascorbic acid cases	Control cases
All persons.....................	526	545	733	721
Registered cases of disease	77	82	68	80
Diseased persons	68	74	63	68
Diseased at least twice	7	8	5	10
of these not reg. as ill	4	5	2	6
reg. as ill	3	3	3	4

Table 2.

Number of persons with »common colds» distributed with regard to the state of the disease and fever.

	Group I.				Group II.			
	Ascorbic acid cases		Control cases		Ascorbic acid cases		Control cases	
	n	%	n	%	n	%	n	%
All persons......	526		545		733		721	
Diseased persons	63	12.0 ± 1.4	65	11.9 ± 1.4	63	8.6 ± 1.0	65	9.0 ± 1.1
State of disease:								
not reg. as ill ..	19	10.2 ± 5.8	20	30.8 ± 5.7	17	27.0 ± 5.6	16	24.6 ± 5.3
reg. as ill ..	44	69.8 ± 5.8	45	69.2 ± 5.7	46	73.0 ± 5.6	49	75.4 ± 5.3
Fever:								
none	29	46.0 ± 6.3	28	43.1 ± 6.1	27	42.9 ± 6.2	29	44.6 ± 6.2
slight	26	41.3 ± 6.2	29	44.6 ± 6.2		47.6 ± 6.3	31	47.7 ± 6.2
moderate	7	11.1	6	9.2	2	3.2	1	1.5
high	1	1.6	2	3.1	3	4.8	2	3.1
unknown........	—	—	—	—	1	1.6	2	3.1
The case is labelled as:								
mild	54	85.7 ± 4.4	50	76.9 ± 5.2	54	85.7 ± 4.4	57	87.7 ± 4.1
medium-severe ..	5	7.9	6	9.2	4	6.3	2	3.1
severe	—	—	1	1.5	1	1.6	—	—
unknown........	4	6.3	8	12.3	4	6.3	6	9.2

Table 3.

Highest temperature observed during the disease.

	Group I		Group II	
	Ascorbic acid cases	Control cases	Ascorbic acid cases	Control cases
Number of cases	55	65	55	57
Temperature in ° C	37.7±0.1	37.9±0.1	37.8±0.1	37.8±0.1

jects (28 and 51 petechiae respectively) and 3 'blue' (23.39 and 75 petechiae respectively). As the curves show, it looks as if the control material did not have very many individuals with 0 and 1 petechia, whereas those with a moderate number (more than 4) were rather more numerous. No significant difference up towards clearly pathological values can be established, however.

Table 4.

Number of persons with other acute infections distributed with regard to the state of the disease and fever.

	Group I		Group II	
	Ascorbic acid cases	Control cases	Ascorbic acid cases	Control cases
All persons................	526	545	733	721
Diseased persons	5	8	—	2
State of disease:				
not reg. as ill	—	1	—	—
reg. as ill	5	7	—	2
Fever:				
none	2	3	—	—
slight	—	2	—	—
moderate	2	2	—	1
high	1	1	—	1
unknown	—	—	—	—
The case is labelled as:				
mild	3	5	—	—
medium-severe..........	2	3	—	—
severe	—	—	—	1
unknown	—	—	—	1

Table 5.

Number of diseased persons distributed with regard to the state of disease and fever.

	Group I Ascorbic acid cases		Control cases		Group II Ascorbic acid cases		Control cases	
	n	%	n	%	n	%	n	%
All persons......		526		545		733		721
Diseased persons	68	12.9±1.5	73	13.4±1.5	63	8.6±1.0	67	9.3±1.1
State of disease:								
not reg. as ill	19	27.9±5.4	21	28.8±5.3	17	27.0±5.6	16	23.9±5.2
reg. as ill ..	49	72.1±5.4	52	71.2±5.3	46	73.0±5.6	51	76.1±5.2
Fever:								
none	31	45.6±6.0	31	42.5±5.8	27	42.9±6.2	29	43.3±6.1
slight	26	38.2±5.9	31	42.5±5.8	30	47.6±6.3	31	46.3±6.1
moderate ..	9	13.2	8	11.0	2	3.2	2	3.0
high	2	2.9	3	4.1	3	4.8	3	4.5
unknown	—	—	—	—	1	1.6	2	3.0
The case is labelled as:								
mild	57	83.8±4.5	55	75.3±5.0	54	85.7±4.4	57	85.1±4.4
medium-severe	7	10.3	9	12.3	4	6.3	3	4.5
severe	—	—	1	1.4	1	1.6	—	—
unknown	4	5.9	8	11.0	4	6.3	7	10.4

c) Morbidity investigations.

We have studied the frequency and course of certain acute infectious conditions in the two groups.

Our intention was in the first place to carry out a statistical treatment of the groups of diseases which can be covered by the heading 'catarrhal complaints', to which we assign: 1) Acute infection of the upper respiratory tract (rhinitis, pharyngitis, laryngitis, tracheitis); 2) Angina tonsillaris; 3) Bronchitis; 4) Pneumonia; 5) Sinusitis; 6) Otitis. We further noted certain other acute diseases of an infectious nature, such as parotitis, vulneral infections, etc. A record was also made of whether the patient was feverish, and to what extent, as also the highest temperature observed during the

Table 6.

Partakers in competition and result of individual fieldcompetition.

	Ascorbic acid cases		Control cases	
	Number	Median[1]	Number	Median[1]
Group I				
All persons.....................	526		545	
Number of partakers	167		187	
» » » , %	31.7±2.0		34.4±2.0	
of these 1. comp.	48	50.0	48	48.5
2. » ....:....	54	49.0	48	52.0
13. » ·	50	62.5	72	61.5
1. plutoon	15	15.0	19	18.0
Group II.				
All persons.....................	733		721	
Number of partakers	190		172	
» » » , %	25.9±1.26		23.9±1.6	
of these 4. comp.	59	57.0	51	53.0
5. »	42	39.5	35	37.0
6. »	34	33.5	32	33.5
8. »	55	56.0	54	50.5

[1] Median signifies the position wich half of the partakers exceeded and half did not attain.

illness. When the period of illness was over, the physician noted down whether he considered the case slight, mediumly serious, or severe. Finally, we registered the number of days the patient was on the sick-list, and how many days, if any, he had been treated in hospital.

When assessing how severe the individual case and the fever are, a certain subjectivity inevitably creeps in, but since the physician did not know to which group the case belonged, and as he examined all cases from both groups, the materials should be comparable.

There were no cases of epidemic influenza during the period of observation. The different kinds of other diseases have each been grouped separately, but field conditions did not permit of sufficiently certain diagnoses to allow of statistical treatment. In any case, the number of cases in the different groups was too small.

An analysis of the material yielded the following results:

In Group I (where the tablets were taken regularly during the entire period of observation) catarrhal infections were contracted by 12.0±1.4 % of the 526 soldiers given 'yellow' ascorbic acid tablets, and by 11.9±1.4 % of the 545 soldiers given 'blue' control tablets. No probable or significant difference between 'yellow' and 'blue' soldiers was to be observed, as regards the character of the fever (tables 1—3). Statistically, the agreement is good.

Over half the cases of illness consisted of acute infection of the upper respiratory tract. The distribution was the same in 'yellow' and 'blue' subjects. As regards other diagnoses, the number of cases was every time too small for statistical treatment; no noteworthy difference was to be observed, however (table 4).

The above conclusions on Group I also apply to the soldiers belonging to Group II; that is to say, those who only took the tablets regularly for the period March 3—April 6.

The tables show that we were in no respect able to obtain any difference for the frequency and course of the registered diseases between the soldiers receiving ascorbic acid and the controls.

d) Testing of the general condition of the soldiers.

With a view to obtaining an idea of the physical and mental condition of the soldiers, we collected the results from individual field competitions for the two groups (i.e. ski-running, shooting, path-finding, judging of distances). We have not been able to show any difference between 'yellow' and 'blue' soldiers in these achievements (table 6).

Discussion.

There is a widespread opinion to the effect that no small part of the Swedish population lives on a diet which, for a great portion of the year, does not provide the necessary Vitamin C. Thus, commenting in 1938 on the report of the Population Commission on the question of nutrition, the Royal Medical Board maintained that large groups of the population within different parts of the country are under-nourished. The so-called Norrland investigation, with others, suggests that the primary deficiency is one of Vitamin C. If this is so, the present scarcity and rise in price of food has further

increased the risk of C hypovitaminotic states. A further contribu-
tion is the fall in the standard of living since, apart from potatoes,
the most important sources of Vitamin C are in the more expensive
foodstuffs.

Our investigations of soldiers, half of whom received for some
months a daily dose of 50 mg of ascorbic acid per person in addition
to the regulation fare, showed that those soldiers not receiving
ascorbic acid suffered from a considerable C Vitamin-deficit, to
judge from the ascorbic acid titrations. Compared with results
and conclusions from earlier publications, our results would seem
to indicate the presence of a C hypovitaminosis, which should be
dealt with by administering ascorbic acid or food rich in Vitamin C.
When these last-mentioned soldiers were compared with those
given ascorbic acid tablets, however, they were found not to suffer
from this 'pathological' deficit, either as regards the frequency of
disease or when tested as to physical or mental condition. In our
opinion, therefore, there is no reason to regard this deficit as patho-
logical, and to complement the diet with extra Vitamin C.

In the investigations prompting the notion of a relatively wide-
spread Vitamin C deficiency, ascorbic acid titrations or capillary
resistance tests have in many cases yielded analysis values deviat-
ing from those considered normal. On the other hand, practically
no attempt seems to have been made, to investigate more closely
whether persons showing a C deficit at the above laboratory tests
differ in any other respect from healthy persons presenting normal
values at ascorbic acid titration and capillary resistance tests. In this
connection we may mention Hultgren's investigation (1933) into
the normal variability in capillary resistance tests, which variabi-
lity proved unexpectedly large. It is possible that factors influencing
the capillary circulation in the skin, such as bodily exertion, diet —
above all, spices — etc., may be of importance here. In any case,
capillary resistance tests did not, in our material, yield any diffe-
rences large enough to indicate incongruities between those who
had been given ascorbic acid and those who had not. Only a few
persons in either group had more than 10 petechiae. This implies
that capillary resistance tests put the occurrence of pathological
Vitamin C deficit in a more correct light than do the ascorbic acid
titrations.

Summing up, it may be stated that earlier publications as to the

Vitamin C standard in Sweden cannot be taken to prove the occurrence of extensive Vitamin C deficit among the population of Norrland or other parts of the country. Our investigations show that, in point of fact, a diet such as that provided in the Swedish army satisfies the demand for Vitamin C, even during that season, spring, when the Vitamin C content of the foodstuffs is lowest.

Our results have been borne out by later investigations by Bergquist (1943) on factory-workers, by Hjärne (1941) on schoolchildren from the country, and by Hammar and Schröderheim (1942) on schoolchildren from Stockholm, all of which have been carried out with control material and statistically analysed. Contrary to what was assumed earlier on, therefore, a Vitamin C deficit sufficient to affect the public health does not seem to be very common in Sweden.

Our ascorbic acid titrations confirm the opinion, often found in present-day literature, that one should not judge the results on the absolute titration values, but should take only the relative values for comparison between different series of experiments within the same investigation. We gave our soldiers 200 mg of ascorbic acid daily from 3—27 March, and 50 mg daily up to May 20 inclusive. The loading tests were begun on May 21 with 300 mg of ascorbic acid daily; not until May 30 did they yield a significant difference between the fasting values and the reduction values 2 hours after taking the tablet. If the deficit obtained from our loading tests is compared with the above-mentioned deficits among soldiers and sailors of certain foreign countries, ours is found to be somewhat higher, though our soldiers were alone in receiving extra ascorbic acid. This example thus shows that titration results obtained from different materials (individuals living in dissimilar milieu) do not immediately lend themselves to comparison.

The results of the individual field competitions showed no difference between soldiers receiving ascorbic acid tablets, and controls. This fact may well have special implications, since an impaired capacity for mental or physical work is thought to be a characteristic symptom of insufficient Vitamin C, and usually precedes scurvy proper.

An increased consumption of Vitamin C takes place during physical labour. If the fare contains insufficient Vitamin C, then an investigation along our lines which concentrates on soldiers to

whom strenuous physical labour is assigned, and who live on a certain standard diet for months, should be able to demonstrate differences in the Vitamin C standard between the ascorbic acid group and the controls. As no difference has appeared, despite the bodily labour, we receive further confirmation of our statement that the diet adopted is satisfactory. Investigating Swiss soldiers for lack of Vitamin C, Demole (1941) found a marked deficit in 57 % of those who had served for 9 months, but in only 10 % of the recruits. Demole explains this partly by the increased physical exertions, which increases the need of the vitamin, and partly by the mass cooking, which is peculiarly adapted to reduce the Vitamin C content of the food.

As was stated in the Introduction, the importance of the Vitamin C as anti-infectious factor has been the subject of lively discussion in the literature of most recent years. Thus, ascorbic acid is considered able to increase immunity in several ways, e.g. by enhancing the bactericidal power of the blood and acting as a cell-stimulating means. According to Peters (1940) and others, Vitamin C does not decrease receptivity to infection, but it is able to have a favourable influence on the course of the disease. Children given extra Vitamin C fell ill as often as other children, but the former recovered earlier.

The presumed power of Vitamin C to increase the body's ability to resist infection has prompted extensive recommendation of extra supplies of ascorbic acid, with a view to preventing catarrhal complaints even in those cases where absolutely no symptoms of deficiency or other signs of disease or weakness were to be found. This idea of Vitamin C as a prophylactic is still very widespread in Sweden, both among teachers and the general public, largely thanks to unreliable medical advertisements from abroad.

On the evidence of our own and other recent Swedish investigations, with trustworthy control material, we do not consider an extra supply of Vitamin C is justified solely on the grounds that the individuals in question show a C deficit in ascorbic acid titrations or capillary resistance tests. The prescribing of extra Vitamin C calls in each case for other symptoms which can be assumed to be associated with C hypovilaminosis, or which usually precede manifest scurvy. In this connection we should like to stress the inadequate familiarity which must still be assumed to obtain for the clinical

Nature of food		Quantities per day						
		1	2	3	4	5	6	7
Dry food								
German sausage, boiled	g	·			40			
» » smoked	»		40					40
Cheese, whole-fat[1]	»	40		40		40	40	
Warm provisions								
Black puddings	»				250		·	250
Brown beans	»			100				
Chocolate, sugared	»	25					25	
Fish, fresh [2]	»						2—300	
Pork, salt or fresh	»			190		110		
Fruit mousse	»		60					
Oats	»	20		20		40		20
Barley kernels	»				10			
Semolina	»		20		20		30	
Sago	»		5					
Sausage, »falu-»	»			210			210	
» German, boiled	»	150						
Meat, fresh	»	275	275		275			225
Timed meat	port.					½		
Red whortle berry jam	g				75			75
Onion powder (or onions)	»		10			10		
Macaroni	»		80				80	
Potato flour	»	15	15	15				15
Wheat flour	»	15			15	30	15	
Horse radish	»				5			
Potatoes	»	500	300	300	300	600	300	100
Herrings, salt	»		200		·			
Syrup	»			10				
Prunes	»		15					12
Dried vegetables	»				12			
Concentrated apple-juice	»		12					10
Peas, green	»					100		
Lentils	»							
Eggs	No.	3						

In addition, daily: Milk, 0.3 l. fresh, or 0.5 l. separated, or corresponding amount of dried milk (ordered). *Dry food:* Bread, hard, 50 g, soft (fine or coarse) 230 g. Butter 20 g, marg. 20 g.

Warm provisions: Bouillon cube, 5 g. Coffee, roasted, 10 g. Lump sugar 25 g, castor sugar 25 g (in 4—5, 20 g). Frying oil 5 g (omitted in 3). Table salt and spices as required.

Alternatives: 1) »Palt»bread 100 g, salt pork 190 g, wheat flour 20 g, replaces midday meal (or: dinner) in 3 every other week.
2) Smoked pork 150 g, may, when available, be exchanged for the 190 g salt pork in 3.
3) Salt meat 250 g, exchanged when supplies permit for fresh meat 275 g.
4) Dried blueberrries 15 g, for blueberry soup exchanged for fruit soup when supplies permit.
5) When eggs are scarce, these and 200 g potatoes are omitted in 1, being replaced by 100 g green peas.

[1] Half-fat cheese, 50 g per portion.
[2] The size of the fish portions depends on whether the fish is served whole in fillets.

Supplement 2. Food list 15/2—14/3 1941.

Nature of food		Quantities per day						
		1	2	3	4	5	6	7
Dry food								
German sausage, boiled	g				40			40
» » smoked	»		40					
Cheese, whole-fat¹	»	40		40		40	40	
Warm provisions								
Black puddings	»				250			250
Brown beans	»		100					
Chocolate sugared	»						25	
Fish, fresh²	»						2—300	
Pork, salt or fresh	»		50	200		125		
Fruit mousse	»			60				
Oats	»	20		20		40		20
Barley kernels	»				10			
Semolina	»		20		20		30	
Sago	»		5					
Sausage, »falu-»	»			210			210	
» , pork	»					210		
» breakfast	»	150						
Meat, fresh	»	275	225		275			225
Red whortle berry jam	»				75			75
Onion powder	»		5					
Macaroni	»		80				80	
Potato flour	»	15	15	15				15
Wheat flour	»	15				15	30	15
Horse radish	»					5		
Potatoes	»	300	300	300	300	600	300	100
Fruit juice	»		30					
Herrings, salt, or mackerel, or .salt Baltic herrings	»		200					
Syrup	»				10			
Prunes	»		15					
Dried vegetables	»					10		10
Peas, green	»	100						10
Lentils	»					100		
Apples, dried	»	40						

In addition, daily: Milk, 0.3 l. fresh, or 0.5 l. separated, or corresponding amount of dried milk. *Dry food:* Bread, hard, 50 g, soft 230 g. Butter 20 g, marg. 20 g.

Warm provisions: Bouillon cube 5 g (omitted in 1). Coffee substitute 10 g. Lump sugar 25 g. Castor sugar 25 g (in 4—5, 20 g). Frying oil 5 g (omitted in 3). Table salt and spices as required.

Alternatives: 1) »Palt«bread 100 g, salt pork 190 g, wheat flour 20 g, replaces midday meal in 3 every other week.
2) Salt meat 250 g, exchanged for fresh meat 275 g, when supplies permit.
3) Dried blueberries 15 g, for blueberry soup exchanged for fruit soup when supplies permit.
4) When eggs are plentiful, 3 eggs and 200 g of potatoes are substituted in 1 for 100 g green peas.

¹ Half-fat cheese, 50 g per portion.
² The size of the fish portions depends on whether the fish is served whole or in fillets.

Supplement 3. Food list 15/3—29/4 1941.

Nature of food		Quantities per day						
		1	2	3	4	5	6	7
Dry food								
German sausage, boiled	g			50		50		
» » smoked	»	50						
Cheese, whole-fat [1]	»		40		40		40	40
Warm provisions								
Black puddings	»	250			250			
Brown beans	»		100					
Fish, fresh [2]	»						2—300	
Pork, salt or fresh	»		200			125		50
Fruit mousse	»					50		60
Oats	»	20		20		40		20
Barley kernels	»				10			70
Semolina	»				20		20	
Rice	»						40	
Sago	»		5					
Sausage, »falu-» or polony	»						210	
» , pork	»			210				
» , »stång»-	»		210					
Meat, fresh	»	275			275			75
Tinned meat	port.			½				1
Red whortle berry jam	g	75			75			
Onion powder	»	5				5		
Macaroni	»						80	
Potato flour	»	15	15	15				15
Wheat flour	»		25		15	100		15
Horse radish	»				5			
Potatoes	»	300	300	300	300	300	300	600
Raisins	»		10					
Fruit juice, sour	»		30					
Herrings, salt, or mackerel, or salt Baltic herrings	»				200			
Syrup	»		10					
Prunes	»	15						
Dried vegetables	»				10			
Peas, green	»			100				
Lentils	»					100		
Apples, dried	»	25						

In addition, daily: Milk, 0.3 l. fresh, or 0.5 l. separated, or corresponding amount of dried milk. *Dry food:* Bread, hard, 50 g, soft 230 g. Butter 20 g, marg. 20 g, or marg. mixed with butter 40 g.

Warm provisions: Coffee substitute 10 g. Lump sugar 25 g. Castor sugar 25 g (in 4, 20 g). Frying oil 5 g. Table salt and spices as required.

[1] Half-fat cheese, 50 g per portion.
[2] The size of the fish portions depends on whether the fish is served whole or in fillets.

Supplement 4. Food list 30/4—31/5 1941.

Nature of food		Quantities per day						
		1	2	3	4	5	6	7
Dry food								
German sausage, smoked	g						50	
Cheese, whole-fat [1]	»	40	40	40	40	40		40
Warm provisions								
Black puddings	g	250			250			
Brown beans	»	100						
Bouillon cube	»			5				
Fish, fresh [2]	»						2—300	
Pork, salt or fresh	»	200	100			100	50	
Fruit mousse	»		50			50		
Oats	»	20		·10		20		20
Barley kernels	»			10				
Semolina	»				20		70	
Rice	»						20	·40
Sausage, »falu-» or polony	»							180
», pork	»				200			
», »stång-»	»		180					
Meat, fresh	»						75	150
Tinned meat	port.			1		½		
Red whortle berry jam	g	75			75			
Union powder	»			5		5		
Macaroni	»							
Potato flour	»	15			15			80
Wheat flour	»		125			100		10
Potatoes	»	350		700	350	350	700	300
Raisins	»	5						
Fruit juice	»							20
Herrings, salt, or mackerel, or salt Baltic herrings	»			175				
Syrup	»	10						
Prunes	»	15						
Dried vegetables	»			10				
Lentils	»		100			100		10
Peas, green	»			5				
Apples, dried	»	20						5
Milk, fresh [3]	dl			3			3	
», separated [3]	»	5	8	2	5	8	7	8

In addition, daily: Dry food: Bread, hard, 50 g, soft 230 g. Marg. mixed with butter, 40 g.

Warm provisions: Chocolate, sugared, 25 g. Coffee mixture 10 g. Lump sugar 25 g. Castor sugar 25 g. Frying oil, 5 g. Table salt and spices as required. Packets of ready-mixed spices not allowed to be issued.

[1] Half-fat cheese, 50 g per portion.

[2] The size of the fish portions depends on whether the fish is served whole or in fillets.

[3] With gruel, 3 dl sep. milk, with chocolate 2 dl sep., with »fruit-creams» 3 dl sep., with balter pudding, 3 dl sep. with rice pudding (in the cooking) 2 dl sep., for porridge 3 dl fresh. Dried milk 10 g = 1 dl milk (substituted as required).

course of C hypovitaminosis, as also the consequent obstacles to its satisfactory diagnosis.

We should like to emphasize that the aspects presented here as to the administration of ascorbic acid for prophylactic ends apply to large groups of persons. When it comes to the individual case, the physician has to study other aspects, also, which fall outside the scope of this investigation.

The material investigated is large enough for the agreement found to be regarded as fairly conclusive proof. It is, of course, not out of the question that a still larger material might yield differences, but even if it did, they could not be large ones: otherwise they would already have appeared in our investigation.

Summary.

In order to establish whether Vitamin C has a preventive effect on common colds, conscripts in the North of Sweden were given tablets from March 3rd to May 31st, 1941, half the number receiving strong doses of Vitamin C, and the other half inactive tablets. The groups were chosen at random (odd and even numbers). A definite difference between the categories with regard to the 'Tillman test' was established both at the beginning and the end of the period.

No difference could be found as regards frequency or duration of colds, degrees of fever, etc. Military competitions, arranged to relieve the tedium, disclosed no difference between the two groups. Thus, the soldiers who only received the diet of the Swedish army, and who showed a 'pathological deficit', did not differ in any respect from those who had been given ascorbic acid during the entire period of investigation. Consequently, there is no reason to assume Vitamin C to be at all instrumental in preventing colds when supplementing the degree of vitamin deficiency existing among soldiers in the North of Sweden.

Recent investigators working on our principles have shown that our conclusions also hold for other groups of the Swedish population.

The fact that an individual has a Vitamin C deficit does not necessarily mean that he must show symptoms of disease, or that

he has an impaired constitution, with an increased disposition to diseases. Special investigations are required to establish how great a vitamin deficit must be to set up trouble of some kind. The problem is not easy to solve, for one thing because the limit between health and sickness may be at a different Vitamin C level for different individuals. The fact that certain groups of the Swedish population show a Vitamin C deficit during certain parts of the year does not, however, imply that their vitamin supply is below the limit for a normal state of health. This investigation has established that the vitamin C deficiency in a group of the population, living under particularly unfavourable circumstances, does not descend to the pathological.

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Physiologic Variations in the Iron Content of human Blood Serum.

I. The Variations from Week to Week, from Day to Day and through twenty-four Hours.

By

KNUD HØYER.

(Submitted for publication June 30, 1944).

Using the method of analysis developed by Broechner-Mortensen & Olsen (1), I have previously determined the iron content in the blood serum of 50 normal men and 50 normal women, all with normal blood picture, and found the average value to be:
in men, 131.2 ± 4.2 micrograms per 100 cm³ of serum; standard deviation, 30.0 micrograms per cent;
in women, 114.8 ± 4.3 micrograms per 100 cm³ of serum; standard deviation, 30.6 micrograms per cent.

The iron content varied in men from 63 to 189 micrograms per cent, in women from 69 to 197. In both sexes, the distribution was normal. The variation from one individual to another is thus considerable; which also agrees with the results come to by other workers.

An investigation like this is, of course, of some interest; still it must seem more important to get established to what extent the iron level in the blood serum is shifted in the individual under varying physiologic conditions. Considering the rather great number of studies on the behaviour of the serum iron under pathologic conditions that have appeared in the literature in recent years, it is surprising to find that so few deal with its physiologic fluctua-

tions. The only authors who seem to have given any particular attention to this side of the question are Vahlquist (10, 11) and Moore, Minnich & Welch (7), to whose studies I shall refer in the following.

In my preliminary investigation, I have myself found considerably greater variations in the serum iron level in the individual normal subject than would be expected from the statements in the literature. I have therefore deemed it necessary to examine this question a little more closely before proceeding to a study of the serum iron in disease.

A. — Variations in Serum Iron from Week to Week in normal Subjects.

Determinations of the iron content of the serum were during a period of three months made once a week on 8 normal men and 12 normal women. The blood samples were drawn between 8 and 9 a.m., and the analyses were made with the use of my own modification of Broechner-Mortensen & Olsen's method, previously described (5). It has a standard error of 2—3 per cent, and may therefore be considered as sufficiently reliable. Hemoglobin determinations and red cell counts were made at suitable intervals, and only slight variations found.

The curve *Fig. 1* shows how the serum iron level shifted in a subject during the 3-month period. Differences between minimum
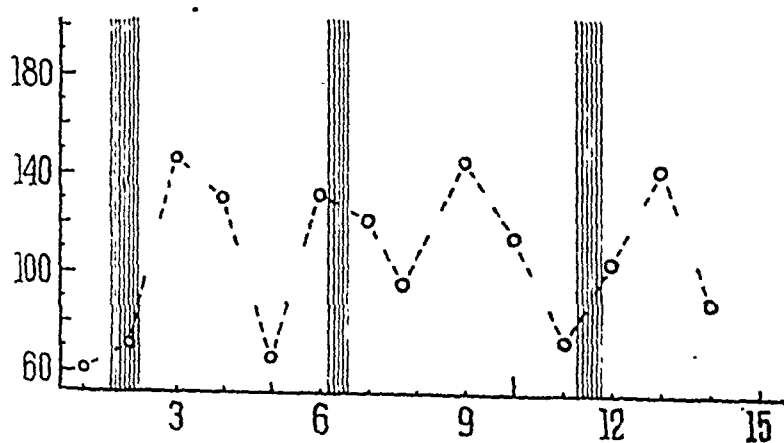
Fig. 1. — *Variations in serum iron from week to week during a 3-months period in a normal woman.* Ordinate - serum iron, in micrograms per cent; abscissa = experimental period, in weeks. Hatched columns = menstrual periods.

Table I.

Minimum and maximum values for iron content of serum in 8 normal men and 12 normal women, determined by weekly tests for 3 months.

Subject No.	Sex	Number of determinations	Serum Iron (micrograms per cent)		
			Minimum	Maximum	Divergence
1	male	14	103	177	74
2	»	12	63	197	134
3	»	14	69	153	84
4	»	13	93	203	110
5	»	14	94	163	69
6	»	13	74	165	91
7	»	13	84	186	102
8	»	13	88	180	92
9	female	12	95	178	83
10	»	12	73	178	105
11	»	12	77	153	76
12	»	14	69	162	93
13	»	14	119	196	77
14	»	14	61	146	85
15	»	14	86	169	83
16	»	15	64	167	103
17	»	15	63	165	102
18	»	13	80	172	92
19	»	15	67	147	80
20	»	8	80	173	93

and maximum values varied in the different subjects, and no correlation with phases of the menstrual cycle could be made. This agrees with what has been found by the majority of previous investigators [Locke, Main & Rosbash (6), Moore, Minnich & Welch (7), Skouge (9), Vahlquist (10), Broechner-Mortensen & Olsen (1)], but is contrary to the findings of Guthmann, Brueckner, Ehrenstein & Wagner (2).

From *Table 1* it will be seen how greatly the iron content of the serum may vary in the individual. The differences between minimum and maximum values for individual subjects averaged in the men 94.5 micrograms per 100 cm³ of serum, in the women 89.3 micrograms. These considerable variations are particularly noticeable in view of the fact that Moore, Minnich & Welch (7) in

Table II.

Average serum iron values in 8 normal men and 12 normal women observed with weekly determinations during 3 months.

Subject No.	Sex	Number of Determinations	Serum Iron (micrograms per cent)		
			Average	Standard Error on Average	Standard Deviation
1	male	14	139.6	6.0	22.4
2	»	12	137.8	12.6	43.7
3	»	14	114.1	6.8	25.4
4	»	13	131.8	9.8	35.6
5	»	14	127.1	5.6	21.0
6	»	13	126.5	7.1	25.8
7	»	13	121.5	8.5	30.9
8	»	13	136.5	8.7	31.4
9	female	12	130.8	8.3	28.4
10	»	12	122.2	8.6	29.9
11	»	12	103.5	7.1	24.4
12	»	14	109.4	6.8	25.6
13	»	14	159.4	6.2	23.0
14	»	14	106.4	8.2	30.7
15	»	14	123.9	6.7	25.0
16	»	15	94.2	7.7	29.8
17	»	15	110.2	8.5	33.0
18	»	13	113.6	6.6	23.8
19	»	15	105.4	5.8	22.5
20	»	8	127.4	9.5	27.0

a series of four-weekly determinations, continued for six months, in 16 normal Freshman college women found only variations half as wide (average, 41 micrograms per cent; maximum, 64 micrograms per cent). Their analyses were made by colorimetric determination with thiocyanate, after wet ashing of the plasma.

Also Vahlquist (10, 11) has shown that the serum iron content can vary considerably in normal subjects. Using a modification of Heilmeyer & Ploetner's method, he made in the course of four weeks from 3 to 5 determinations, 2 of them at twenty-four hours' interval, on 17 men and 15 women, and found rather wide differences, though not as wide as those observed by me.

Table II shows the standard deviation from the individual mean. It averages 29.5 micrograms per cent in men, 26 micro-

grams per cent in women. *The variations are thus at repeated determi-*
nations at intervals of 1 week on the individual normal subject of
about the same magnitude as at single determinations on several diffe-
rent normal subjects.

B. — Variations from Day to Day and intra Diem in normal Subjects.

The literature contains only few and incomplete statements
respecting the variations that occur in the serum iron level in nor-
mal subjects during the daily cycle. Vahlquist (11) made deter-
minations on 15 men at 8 a.m. and 6 p.m. the same day, and at
8 a.m. the following day, and found an average decrease in the
evening, of 36.3 ± 9.2 micrograms per cent; with a variation between
$+ 40$ and $- 90$ micrograms per cent. Only one set of observations
was made on each subject. Moore, Minnich & Welch (7) plotted a
24-hour curve from determinations on 6 or 7 blood samples taken
at intervals during that period on a not specified number of normal
subjects, some of whom were hospital patients. Only on one of them
were 2 sets of observations made, at intervals of 1 week. The fluc-
tuations observed were slight, — of 20 to 35 micrograms per cent
— and had no persistent directional characteristics. Nilsson (8)
has in connexion with other investigations published a single 24-
hour curve for serum iron in a normal subject, which shows a decrea-
se at night, followed by increase the next morning. Hemmeler (4)
does not give any details of his investigations, but merely says
that »le fer sérique subit, chez un sujet normal, des variations impor-
tantes au cours des 24 heures, dans le sens qu'il suit un rythme
journalier, atteignant son minimum le soir et son maximum le
matin.» These are, so far as I have been able to find, the only
existing studies on the intra diem fluctuations of the serum iron
and I have therefore felt prompted to undertake some new inves-
tigations in order to shed light on this question, the elucidation of
which is of fundamental importance for the evaluation of serum
iron determination in clinical work.

My own observations were made on 12 normal subjects, 6 men
and 6 women. On each of these, 68 blood samples were drawn
throughout a period of 5 weeks, for analysis after the following
scheme: 1) a sample every morning for 14 days in succession; 2)
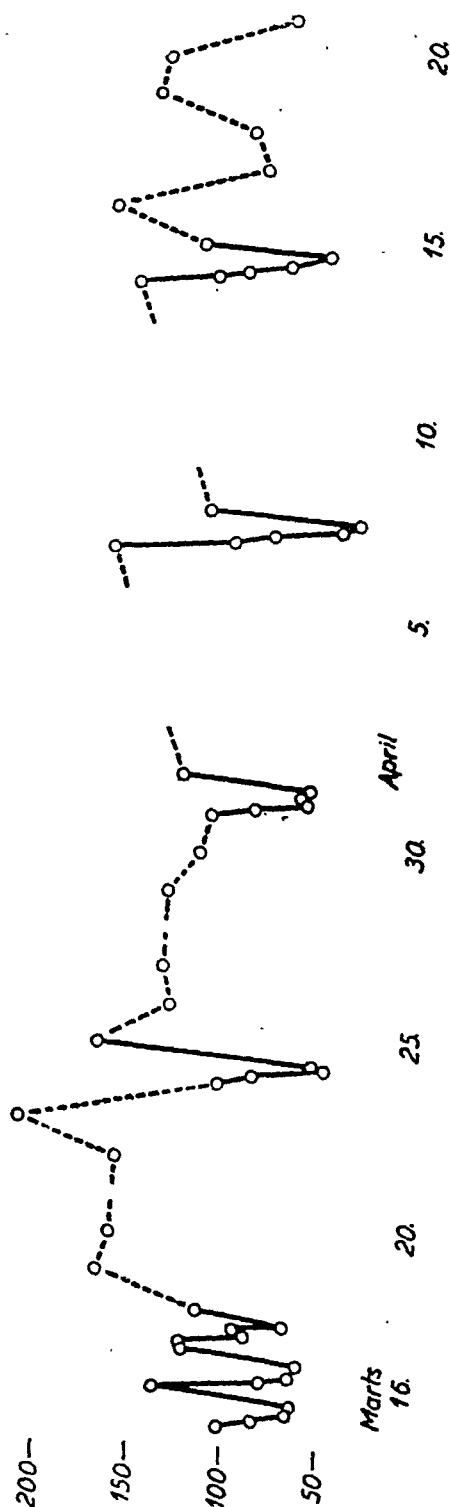
Fig. 2. — *Variations in serum iron during 5 weeks in a normal subject;* 68 determinations in all. The dotted curve shows the variations from day to day, the solid curve the fluctuations intra diem. Ordinate = serum iron, in micrograms per cent.

plotting of 7 24-hour curves for each subject on the basis of samples taken respectively at 8 a. m., noon, 4, 8 and 11 p.m. and 8 a.m. the following day; 3) a sample at 8 a.m. and another at 8 p.m. for 8 days in succession, for comparison of the morning- and evening iron values.

To guard against any source of error that might be the result of so many blood-drawings (a serum iron analysis with double determination requires 3 cm³ of serum), I divided the subjects under observation into two groups, of six each, and carried the experiment through in opposite order with the two, so that in one of them most of the samples were taken in the beginning of the experimental period, in the other during its latter part. Hemoglobin determinations and red cell counts were made every week and showed no noticeable variations during the whole period.

As already said, the standard error in serum iron determinations is between 2 and 3 per cent. Technical errors from the blood-taking itself, and from the different manipulations with the blood and serum before the analyses are made, were ensured against by aspiring, with a glass syringe and several of the needles used for the blood-taking, a number of samples from the same serum and treating them in the same manner as ordinary blood samples (centrifuging, pipetting-off, etc.). At the following iron analyses, the same serum iron value was found in all the serum samples.

1. Variations from Day to Day.

On each of the twelve subjects, 26 determinations were made, 14 of them at intervals of only 1 day. The blood samples were in all cases taken at 8 a.m., before breakfast.

As *Table III* shows, the serum iron level also varied considerably from day to day in the individual subject. The divergences ranged from 59 to 142 micrograms per cent and averaged 105.3 micrograms per cent for the group. The standard deviation from the individual mean is thus great (see *Table IV*), averaging in the men 27.8 micrograms per cent, in the women 26.0.

As earlier mentioned, Vahlquist (10, 11) in his observations on 17 normal men and 15 normal women (but with only from 3 to 5 determinations on each) in some cases found day-to-day variations as great as those found by me, but on the average smaller. Heil-

Table III.

Minimum and maximum serum iron values in 12 normal subjects, on basis of determinations made in the mornings through 5 weeks.

Subject No.	Sex	Number of Deter- minations	Serum Iron (micrograms per cent)		
			Minimum	Maximum	Divergence
1	male	26	93	184	91
2	»	27	58	149	91
3	»	28	61	203	142
4	»	27	64	169	105
5	»	27	103	211	108
6	»	15	70	158	88
7	female	28	63	170	107
8	»	26	60	161	101
9	»	26	80	213	133
10	»	27	59	192	133
11	»	28	64	123	59
12	»	28	51	159	105

Table IV.

Average serum iron values determined at intervals, at 8 a.m., through a 5-week period, on 6 normal men and 6 normal women.

Subject No.	Sex	Number of Deter- minations	Serum Iron (micrograms per cent)		
			Average	Standard Error on Average	Standard Deviation
1	male	26	128.7	5.0	25.4
2	»	27	112.6	4.5	23.4
3	»	28	127.6	6.0	31.7
4	»	27	123.6	4.6	24.0
5	»	27	160.2	6.4	33.5
6	»	15	106.2	7.4	28.5
7	female	28	113.6	4.5	23.6
8	»	26	95.6	4.6	23.8
9	»	26	136.9	6.0	30.4
10	»	27	103.1	6.3	32.8
11	»	28	97.1	3.9	20.6
12	»	28	104.3	4.7	24.7

meyer & Ploetner (3) and Skouge (9) found by 2 to 3 determina-
tions on 12 normal subjects a maximum scattering of $\pm$ 30 per
cent, and thus considerably smaller variations than those observed
by me.

2. Variations intra Diem.

In order to study the variations in the serum iron level during
the daily cycle, I made determinations on the same 12 normal
subjects at 8 a.m., noon, 4, 8 and 11 p.m. and 8 a.m. the following
day. For each individual, 7 24-hour curves were plotted in this
manner; i.e. 82 curves in all. For reasons of economy of space, the
individual curves are not reproduced.

Table V.

Average serum iron values! (in micrograms per cent) in 12 normal subjects
at different times during a 24-hour period. (Heavy figures = lowest values
during the 24 hours).

Subject No.	Sex	8 a.m.	Noon	4 p.m.	8 p.m.	11 p.m.	8 a.m.	Average Decrease
1	male	134	130	104	74	76	120	60
2	»	124	114	109	94	88	146	36
3	»	92	80	76	76	66	106	26
4	»	135	122	102	94	93	138	42
5	»	119	105	103	93	103	116	26
6	»	173	161	130	122	117	175	56
7	female	114	97	79	83	76	101	38
8	»	131	99	75	69	58	132	73
9	»	104	81	67	70	62	96	42
10	»	102	98	92	87	94	104	15
11	»	118	100	81	62	69	109	56
12	»	117	126	97	75	75	119	42

Table V shows the average values at different times during the
24-hour period, and it will be seen that the level falls in the course
of the day and is lowest in the evening. The decrease, from the
value at 8 o'clock in the morning to the lowest evening value, aver-
aged, for all the curves, 42.7 micrograms per cent. The decrease
was equally great in men and women, and was nearly always fol-
lowed by an increase from the evening value to the next day's
morning value.
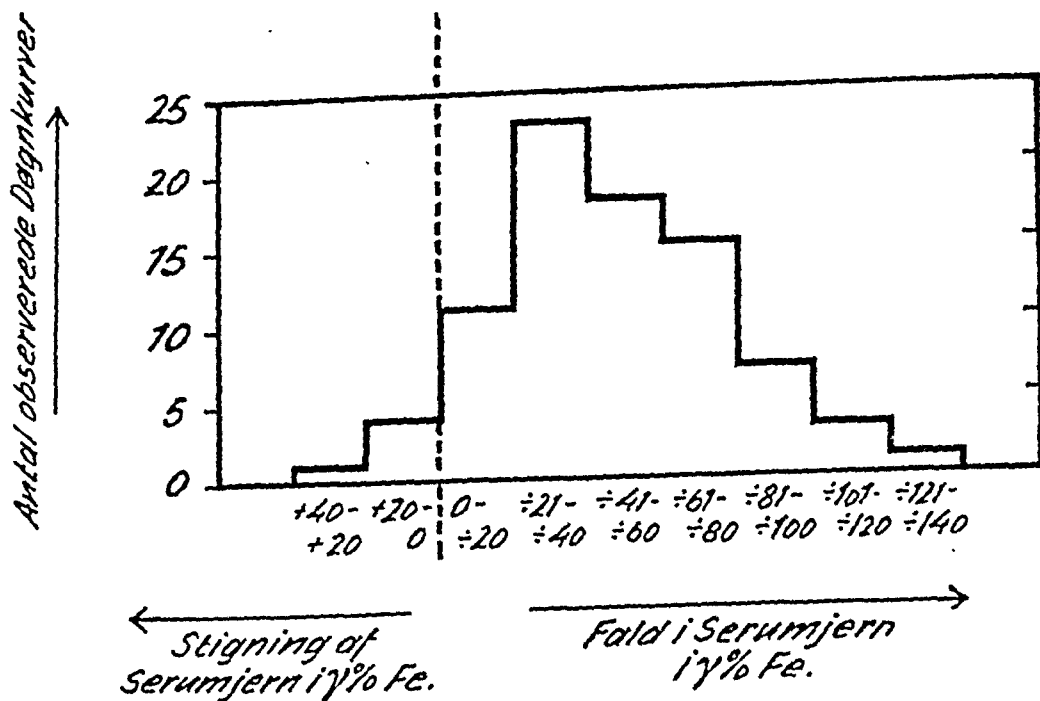
Fig. 3. Distribution of 82 24-hour serum iron curves of normal subjects with reference to highest and lowest levels reached between the hours of 8 a.m. and 11 p.m. of the same day. — To left of zero-line: curves showing increase, to right of zero-line: curves showing decrease, of serum iron during the day.

Sixty-six of the curves showed this fall in the serum iron level in the course of the day; but as it will be seen from *Fig. 3* there was an even transition from these to curves with constant values throughout the 24 hours; — i.e. with fluctuations of less than 20 micrograms per cent. These curves, of which there were 15, were found especially in the cases where the morning values were low. Only one of all the 82 curves showed increase of the values, and this increase was so slight, — 23 micrograms per cent, — that it is not even certain.

As *Figs. 2 and 3* show, the evening drop in the values varied considerably and was in some cases surprisingly great. In 3 of the 82, it was over 100 micrograms per cent (maximum: 131 micrograms per cent). The lowest value was as a rule found at 8 or 11 p.m., but in 11 of the curves already at 4 p.m. In a very few cases there was no increase from the evening level to the level the following morning; on the other hand, there were also cases in which the

increase from evening to morning was greater than the decrease on the foregoing day.

The curves varied not only for the different subjects, but also for the same subject at repeated observations (see Fig. 2). In some orientating studies, 21 curves were plotted, of the intra diem variations in 17 normal subjects. Also in this investigation there was a drop in the serum iron levels between the hours of 8 a.m. and 8 p.m., averaging 42.9 micrograms per cent. At the same time, determinations were made on 20 normal subjects, of the hemoglobin percentage, the number of red cells and their corpuscular volume; in 8 of them also of the serum protein. Of the results of these investigations I will only say that *neither the hemoglobin nor the red cell count showed noticeable fluctuations within the 24 hours; and though slight changes were observed in the serum protein, these had no persistent directional characteristice.* We may therefore conclude that the variations in the serum iron level are independent of these factors.

3. — Comparison of the Morning and Evening Values.

As the 24-hour curves in normal subjects nearly always showed lower evening-than morning values for the serum iron, and the

Table VI.

The serum iron values (in micrograms per cent) at 8 a.m. and 8 p.m. in the same normal subject.

Subject No.	Sex	8 a.m.		8 p.m.	
		Average	Standard Deviation	Average	Standard Deviation
1	male	129.8	25.4	101.0	18.5
2	»	113.1	23.8	99.0	25.5
3	»	129.0	33.6	95.7	23.6
4	»	122.6	20.4	76.7	14.4
5	»	164.8	34.2	112.4	23.7
6	»	108.8	24.0	74.0	8.8
7	female	113.5	17.2	80.6	19.2
8	»	90.4	21.4	84.3	14.2
9	»	123.2	28.6	67.8	15.6
10	»	113.7	40.7	65.1	11.9
11	»	98.4	21.6	63.1	14.9
12	»	101.4	26.8	77.3	20.4
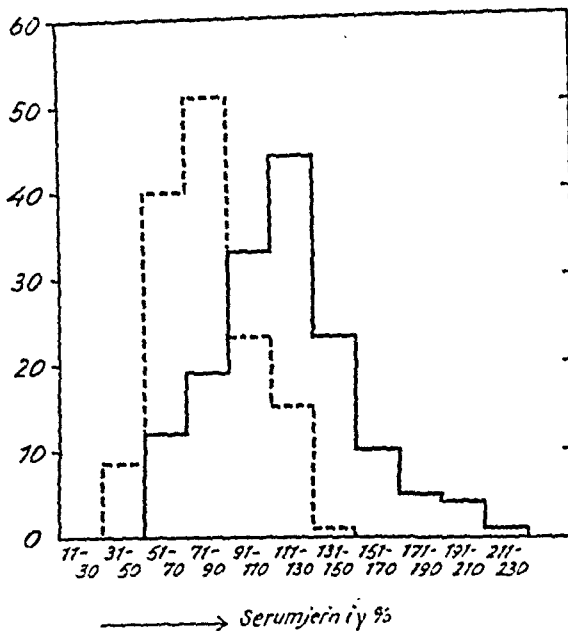
Fig. 4. — Comparison between the serum iron determinations at 8 a.m. and 8 p.m. on the same day, by repeated determinations, in 6 normal men and 6 normal women. The dotted curve showing the distribution of the 8 p.m. values, the solid curve that of the 8 a.m. values. — Abscissa = serum iron, in micrograms per cent.
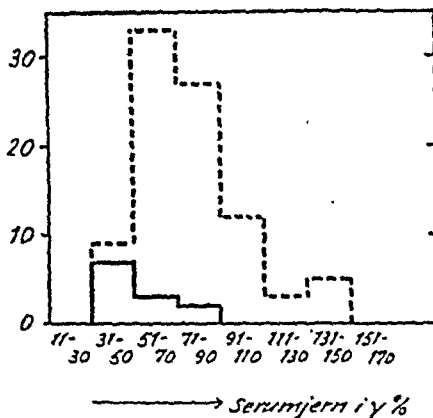
Fig. 6. — Distribution of the lowest serum iron values in 82 24-hour curves of 12 normal subjects (dotted histogram) and of lowest values in the same 12 subjects (solid histogram).

evening values, moreover, lesser changes, it occurred to me that the evening values might perhaps be more or less constant in the individual subject and might perhaps even correspond to the serum iron values under standard conditions in the same manner as, for example, the fasting blood sugar. In order to study this question,

I compared the 8 a.m. and 8 p.m. values in normal subjects, both in the 82 24-hour curves and by determination of the values, on the same 12 subjects, at the same two hours of the day, for 8 to 10 days in succession. The results are shown in *Table VI* and *Fig. 4*.

In *Fig. 5* we see the standard deviation of the lowest serum iron values in the 82 24-hour curves, and that the minima are reached at varying hours of the period. Curiously enough, their deviation is not less than that of the 8 p.m. values (*see Fig. 4*). The solid histogram in *Fig. 5* shows the distribution of the lowest values found in the 12 normal subjects. Here the standard deviation is considerably less.

I have not been able, as yet, to find any explanation of the great variations observed in the serum iron, especially of those during the 24-hour period. The notes made of the mode of life of the twelve subjects during the period of investigation have not given me any clue, because I have not been able to trace any effect on the serum iron content of the blood, either of hard work, diet, time at which the meals were taken or the length of nightly sleep.

Summary.

The author relates the results of his studies on the physiologic variations in the iron content of human blood serum.

A. — *Variations from Week to Week.* Determinations of the serum iron content were during a period of 3 months made once a week on 8 normal men and 12 normal women. The difference between minimum and maximum values in the individual subject averaged in the men 94.5 micrograms per cent, in the women 89.3 micrograms per cent. Variations of that magnitude have not been demonstrated before in normal subjects. The standard deviation from the individual mean averaged in the men 29.5 micrograms per cent, in the women 26.9 micrograms per cent. *The variations are thus at repeated determinations on the individual normal subject of about the same magnitude as at single determinations on several different ones.* The fluctuations in the women had no correlation with phases of the menstrual cycle.

B. — *Variations from Day to Day.* In the course of 5 weeks, 26 determinations were made, in the morning, before breakfast, on 6 normal men and 6 normal women. The average difference between

minimum and maximum values in the individual subject was 105.3 micrograms per cent. The variations were equally great in both sexes. The standard deviation from the individual mean averaged in the men 27.8, in the women 26.0 micrograms per cent. *The variations from day to day are thus of about the same magnitude as the variations from one week to another.*

C. — *Variations intra Diem.* On the same 6 normal men and 6 normal women, determinations of the serum iron content were, in another series of experiments, made at 8 a.m., noon, 4, 8 and 11 p.m. and 8 a.m. the following day, and 7 24-hour curves plotted for each of them; i. e. 82 curves in all. *Sixty-six of these curves showed a fall in the serum iron level from morning till evening.* Calculated on all the curves, this fall averaged 42.7 micrograms per cent; but in some individual cases it was considerably greater, up to as much as 131 micrograms per cent. The lowest values were as a rule found at 8 or 11 p.m., where-upon the level in nearly all cases rose again until the following morning. Fifteen of the curves, however, showed practically constant values throughout the 24 hours; and it was noticeable that this chiefly was the case with the curves of subjects in whom the morning values were low. Only one curve showed a slight, and perhaps not certain, rise in the course of the day. *The 24-hour curves varied not only for the different subjects, but also for the same subject at repeated determinations.* When it is a question of comparing different serum iron values, whether in different normal subjects or in the same subject at repeated determinations, the blood samples should therefore always be withdrawn at the same hour of the day; but even thus there may be a difference in the values, determined by this variation in the 24-hour curves themselves. ·

D. — *Comparison of the Morning- and Evening Values.* The 8 a.m. and 8 p.m. values were compared, both in the 82 24-hour curves and by determinations made on the same 12 subjects, at the same two hours of the day, for 8—10 days in succession. Also the individual 8 p.m. values showed some deviation, though not as great as the 8 a. m. values. The standard deviation of the lowest serum iron values in the 82 curves was not less than that of the 8 p.m. values. *Thus, there is no particular time of the 24-hour period at which it may beforehand be expected that the serum iron will have reached its lowest level.*

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Physiologic Variations in the Iron Content of human Blood Serum.

II. Further studies of the intra diem variations.

By

KNUD HØYER.

(Submitted for publication June 30, 1944).

In a previous paper (1) I reviewed the studies of other authors and described my own investigations concerning the variations which occur in the iron content of the human blood serum of normal subjects during the daily cycle; and I showed that normally there is a considerable fall of the iron level from morning till evening, followed by a rise to the next morning level.

At the previous plottings of the 24-hour curves, no determinations were made during the night hours; and as it must be of some interest to know at what time of the day or night the serum iron reaches its lowest level, I have made some additional studies with a view to shedding light on this question. The experiments were made on 20 normal subjects (9 men and 11 women), who all on hematologic examination showed normal values and normal sedimentation rate. None of them had recently had colds or any infectious disease. During the 24-hours of the experiment, they attended to their usual work, ate their usual meals and slept from 11 p. m. to 7 a. m. The samples of blood were drawn at 8 a m., noon, 4, 8 and 11 p. m., 2, 5 a. m. and at 8 o'clock the following morning.

As seen from *Table I* and *Fig. 1*, none of the curves showed any rise of the serum iron from the morning level. On the contrary, 18 of them show a distinct fall, and only 2 of them a practically

Table I.

Variations in serum iron during a 24-hour period in 20 normal subjects. Values stated in micrograms per cent. (Heavy figures = lowest values during the 24 hours).

No.	Sex	8 a.m.	Noon	4 p.m.	8 p.m.	10–11 p.m.	2 a.m.	4 a.m.	5-6 a.m.	7–8 a.m.	Max. fall
1	male	114	112	100	93	77	*65*		104	147	49
2	»	96	93	93	99	85	*79*		91	139	17
3	»	99	105	89	81	65	*47*	53	62	82	52
4	»	120	118	129	99	89	*80*		88	119	40
5	»	108	106	103	106	77	*58*	*58*	69	92	52
6	female	115	114	121	112	119	*110*		*110*	127	5
7	male	138	137	150	103	108	*86*		88	139	52
8	»	125	123	153	134	102	75	65	*62*	75	65
9	female	140	108	99	96	*54*	56		75	112	86
10	»	144	147	122	110	94	91		*76*	116	68
11	»	119	96	85	73	64	*63*		85	125	56
12	»	133	117	101	78	72	*55*		74	149	78
13	»	109	107	88	70	64	56		*54*	109	55
14	»	116	98	94	67	*63*	70		103	146	53
15	»	115	112	108	*61*	65	72		130	127	54
16	male	156	149	136	129	130	*99*		125	190	57
17	»	225	219	170	145	121	107	111	*106*	131	119
18	female	74	56	54	58	*51*	78		135	172	23
19	»	159	157	157	119	111	*86*		98	169	73
20	»	207	155	87	64	*54*	56		65	125	153

constant level throughout the 24 hours. This accords with the results of my previous studies. But as a result of these new experiments we now also see that the serum iron as a rule (in 15 of the 20 curves) reaches its lowest level at night, during sleep.

Therefore, the decrease in the Serum iron level becomes greater than it was found in my previous experiments, where no determinations were made during the night hours. While the fall from morning till evening was then found to average 42.7 micrograms per cent, we now see that from the morning values to the lowest values observed during the 24 hours there is an average fall of not less than 60.4 micrograms per cent. It is evident that this last figure is the correctest expression for the intra diem variations. *In normal subjects, the serum iron thus shows a characteristic diurnal rythm, with maximum value in the morning and minimum value just after midnight.*
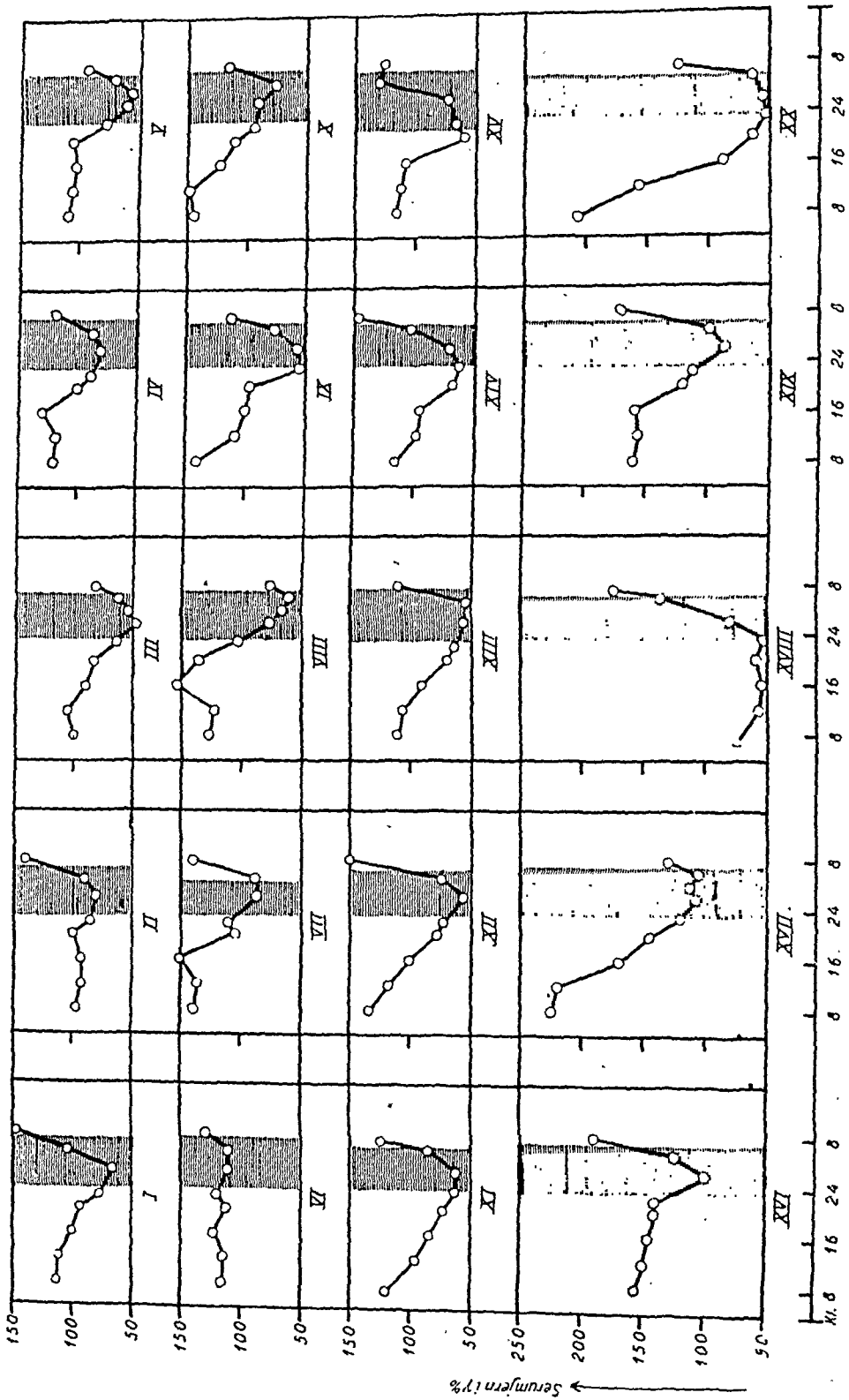
Fig. 1. 24-hour curves of serum iron in 20 normal subjects. Values stated in micrograms per cent. The hatchings indicate the length of the sleep.

Variations during the 24-hour Period in Subjects with Night Work.

After the 24-hour curve for normal individuals working during the daytime had been established, it seemed of interest to examine whether the curve was different for persons who work in the night-hours and sleep during the day. To that end I studied the variations in 10 female hospital nurses who were on night duty for shorter periods at a time, and in 11 others, male and female, who for several years had been working only nights, and who might therefore be assumed to be particularly suitable objects for study of this problem. With regard to the first group, with the shorter periods of night work, the question might perhaps be a little different, because these persons only to a certain extent can adapt their mode of living to the changing working hours; which particularly result in their getting their sleep more or less irregularly. All the twenty-one subjects were hematologically equilibrated, and none of them had recently had any infectious disease. From each of them, 8 blood samples were withdrawn at different times during the 24-hour period, both at night and while they were sleeping during the day. The first sample was taken about an hour after they woke up; the point of time varying somewhat in the individual case

Table II.

Serum iron values (in micrograms per cent) at different times during a 24-hour period in 10 normal subjects for shorter periods engaged in night work. (Heavy figures = lowest values registered during the 24 hours).

No.	Sex	Number of hours after beginning of experimental period								Max. decrease from 1st sample	Duration of sleep (hours)
		1	4-6	8-9	12-15	16-17	19-21	22-23	24-27		
1	male	112	114	116	112	86	*71*	72	76	41	8
2	female	84	84	81	73	59	*42*	53	73	42	9
3	»	59	57	56	48	49	*45*	65	80	14	6
4	»	72	104	105	·96	78	*45*	65	101	27	9
5	»	107	108	105	*96*	*96*	100	*96*	146	11	7
6	»	146	115	100		74	*66*	99	114	80	7
7	»	102	93	100	96	88	63	*54*	110	48	10
8	»	109	104	79	77	77	*72*	85	111	37	9
9	»	139	133	127	86	90	*75*	81	152	58	9
10	»	125	156		85	116	69	*62*	112	63	7
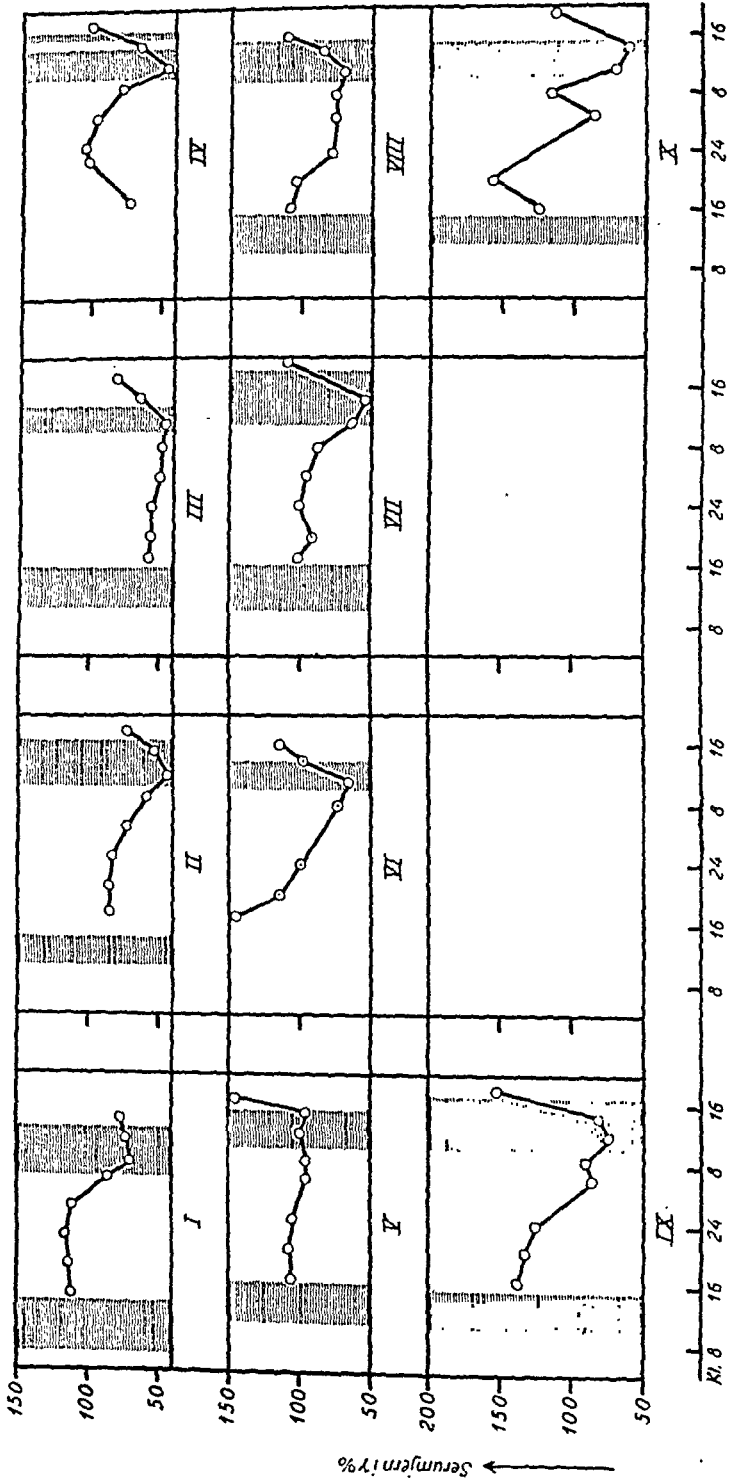
Fig. 2. 24-hour curves of serum iron in 10 normal females, for a shorter period engaged in night work. Values stated in micrograms per cent. The hatchings indicate the length of the sleep.

according to the person's practiced habits with regard to sleeping time. The results of the experiments are shown in *Tables II and III*, and in the graphs *Figs. 2* and *3*.

As *Table II* and the curves in *Fig. 2* show, the serum iron level in most of the cases (8 of the 10) reached its highest in the afternoon, immediately after wakening, whereupon it gradually fell during the night and the following forenoon, and then rose again during the last part of the sleep in the afternoon. Variation in the opposite direction was not seen in any of the cases, but in 2 of the subjects the values were practically constant during the entire 24-hour period. The average decrease in the serum iron level, calculated with the first determination after waking as basis, was 38.0 micrograms per cent. The lowest values were in nearly all the cases found at a time corresponding to a couple of hours after the beginning of sleep. From then on, the values increased during the latter part of the sleep and reached their maximum immediately after waking. The average duration of the sleep was about 8 hours. Even during a brief sleep the serum iron level may fall considerably. Thus, the duration of the sleep does not seem to have any influence on the serum iron level.

For 3 of the subjects who lent themselves to this experiment, 24-hour serum iron curves had already been plotted before, at a time when they worked during the day and slept at night, and in
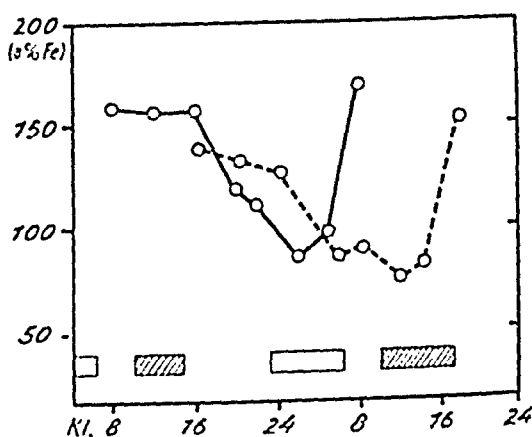
Fig. 3. 24-hour curves of serum iron in the same normal individual, at first on day work (the solid curve), later on night work (the dotted curve). Values stated in micrograms per cent. (The empty columns indicate the length of the sleep when on day work, the hatched columns when on night work.).

Table III.

Serum iron values (in micrograms per cent) at different times during a 24-hour period in 11 normal subjects who had for several years been working nights. (Heavy figures = lowest values observed during the 24 hours).

No.	Sex	Number of hours after beginning of exp. period								Max. decrease from 1st sample	Duration of sleep (hours)	No. of years on night work
		0—3	4—6	8—11	12—14	15—18	18—22	20—23	23—27			
1	male	109	100	91	79	91	*73*	98	131	36	8	18
2	»	89	83	*63*	71	92	95	114	132	18	7	1.5
3	»	109	102	65	*47*	55	47	92	112	62	9	15
4	»	73	77	104	97	70	49	*48*	74	35	9	7
5	female	93	94	68	72	82	78	*67*	109	25	8	16
6	»	116	117	97		*80*	81	95	138	36	4	16
7	»	88	80	75	63	62	*61*	84	112	26	5	1.5
8	male	110	122	112	88	73	*67*	83	111	43	7	5
9	»	58	58	51	56	53	*43*	53	93	15	5	4.5
10	»	58	59	62	53	47	*45*	56	72	13	7	5.5
11	»	72	62	38	46	39	*37*	62	67	35	6	11

all of them the curve changed considerably when they changed to night work. *Fig. 3* shows the two curves for one of these subjects.

Table III and *Fig. 4* thus show exactly the same variations as the foregoing. Also in these subjects the serum iron reached its highest level immediately after waking, its lowest a couple of hours after the person had gone to sleep. Two of the curves showed constant values throughout the 24-hour period. The average decrease, from the first blood sample to the lowest value, was 31.3 micrograms per cent, or very nearly the same as in the case of the other group. The duration of the sleep had no influence on the serum iron.

If we sum up the results of all these observations, we see that in the 21 normal subjects with night work there was an average fall in the serum iron level, of 36.4 micrograms per cent, calculated from the highest value immediately after waking to the lowest registered during the 24-hour period. *It is thus established that the diurnal rhythm of the serum iron in normal subjects working nights and sleeping during the daytime changes, so that the highest level is reached in the evening immediately after waking, the lowest in the forenoon a couple of hours after the person has gone to sleep.*
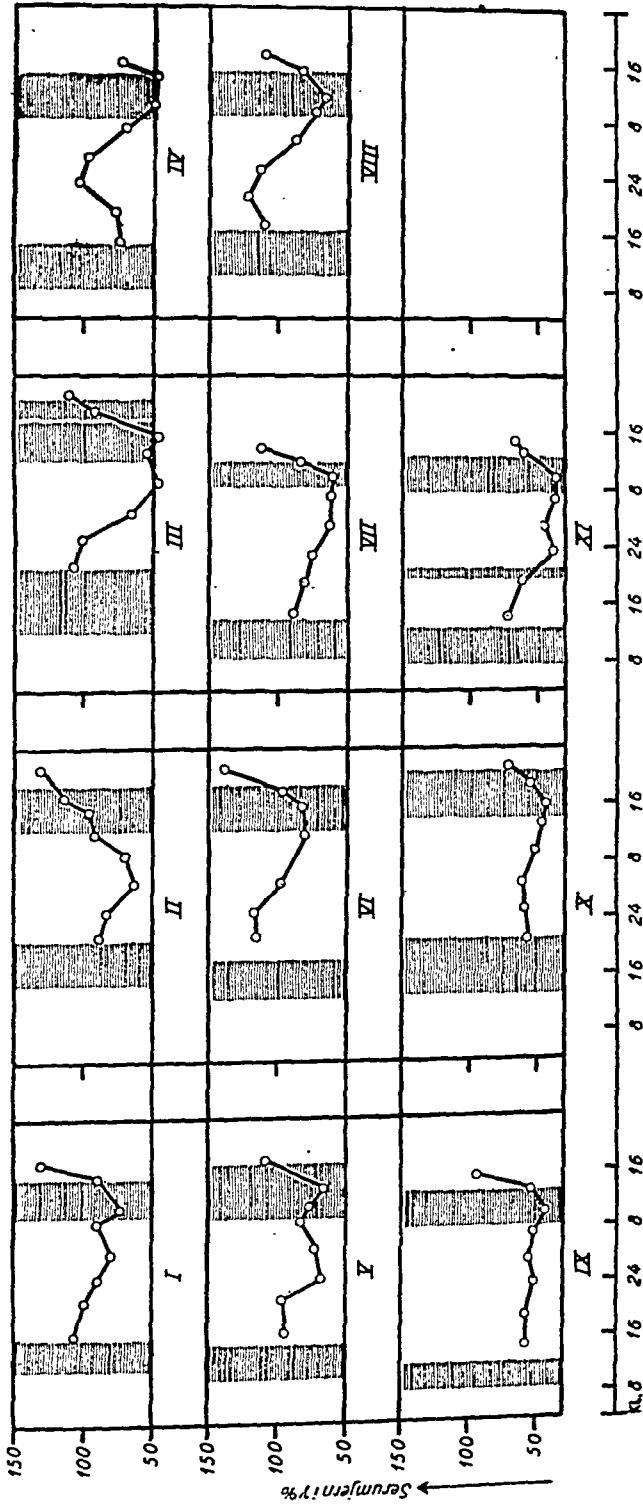
Fig. 4. 24-hour curves of serum iron in 11 normal subjects, for several years on night work. Values stated in micrograms per cent. Duration of the sleep indicated by the hatched columns.

Finally, I have on 33 subjects, working nights, made 3 determinations of the serum iron at intervals during a 24-hour period, namely in the evening immediately after waking, the next morning immediately before the person went to sleep and again the same evening immediately after he woke up. In these experiments, I found a fall in the serum iron level from the first blood sample to the second, which averaged 23.7 micrograms per cent. My only purpose with the experiment was to get it established on as large a material as possible that the intra diem variations of the serum iron level in subjects on night duty follow a different rhythm from the one observed in those who work in the daytime. That the demonstrated fall is less than the one shown in the foregoing experiments is because no determinations were made during sleep, when the serum iron, as we know, as a rule reaches its lowest level. But the direction of the variations is the same as previously shown.

It may perhaps seem surprising that the altered 24-hour curve for the persons on duty at night shows a fall considerably less than that of the persons on duty in the daytime. A contributing cause may *possibly* be that the work of the former is of a more quiet, chiefly sedendary character. In a series of studies, which will be published later, I have in normal subjects found a considerable fall of the serum iron level after cessation of muscular work; and it is not impossible that muscular effort may be a factor influencing its intra diem variations.

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Über die Veränderungen des Sternalpunktates und des Blutbildes bei der akuten und chronischen hämatogenen Osteomyelitis.

Von

E. TIITINEN, Vilppula, Koliniemi, Finnland.

Aus dem mir zugänglichen Schrifttum habe ich nicht entnehmen können, dass die Reaktion des Knochenmarks bei der akuten und chronischen hämatogenen Osteomyelitis untersucht worden wäre. Rohr (1940) bemerkt sogar, dass dieser Umstand noch unaufgeklärt sei. Deswegen hatte ich die Absicht, im folgenden vor allem zu untersuchen, ob die hämatogene Osteomyelitis eine stärkere als die bei Infektionen gewöhnliche Reaktion im Knochenmark hervorruft, oder ob die durch sie erzeugten Veränderungen den im allgemeinen bei akuten Infektionen vorkommenden Veränderungen an die Seite zu stellen sind. Mit Rücksicht auf den vermehrten Gebrauch der Sulfonamide ist auch die genaue Verfolgung des Blutbildes wichtiger als zuvor geworden.

Die Reaktion des Knochenmarks bei Infektionen hat schon früh den Gegenstand von Untersuchungen gebildet. Rubinstein (1901) wies experimentell nach, dass bei Entzündungen, die mit einer Leukozytose verbunden sind, die segmentkernigen Leukozyten des Knochenmarks sich zunächst verringerten, später die Myelozyten an Zahl zunahmen und schliesslich beim Abklingen der Infektion die reiferen Formen sich wieder vermehrten. Kankaanpää (1916) konnte experimentell feststellen, dass sich die Myelozyten während der

ersten Tage nach der Infektion vermehrten, wogegen zumal bei Streptokokkeninfektionen die segmentkernigen Leukozyten abnahmen, um später wieder zuzunehmen, sodass sie 2—3 Wochen nach der Infektion wieder vorherrschend wurden.

Später sind akute Infektionen in dieser Beziehung insbesondere von Barta (1933), Nordenson (1935), Klima (1938) und Rohr (1940) untersucht worden. Barta unterscheidet 5 verschiedene Reaktionstypen, die von der Infektionsstärke abhängen. Je stärker die Infektion ist, um so mehr nehmen die unreiferen Zellen an Zahl zu, und wenn vor allem die Promyelozyten reichlich vermehrt sind, liegt nach Barta eine sehr starke Reaktion vor. Nordenson und Klima betrachten die entzündliche Reaktion als stark, wenn die gemeinsame Menge der Myelozyten und Promyelozyten im Knochenmark 30 % übersteigt. Rohr unterscheidet drei Reaktionstypen, die stabkernige, die myelozytär-metamyelozytäre und die vorwiegend promyelozytäre Reaktion, welch letzterwähnte bei schweren akuten Infektionen auftritt. Bei Pneumonie und Pleuraempyem z. B. hat Rohr 23 % Promyelozyten im Knochenmark zählen können. Die Myeloblasten nehmen nicht an dieser Reaktion teil, ihre Zahl hat selten 2 % überstiegen, und die Zahl der Mitosen ist kaum vermehrt. Die Lymphozyten und segmentkernigen Leukozyten sind stark vermindert. Bei chronischen Infektionen und langwierigen Eiterungen ist die Reaktion des Knochenmarks in der Hauptsache stabkernig. Im Kindesalter sind alle leukozytären Reaktionen nach links in der sog. unreiferen Richtung verschoben (Anselmino 1926). Virkkunen (1943) hat in einigen Anginafällen eine verhältnismässig starke Reaktion festgestellt, indem sich die Gesamtmenge der Myelozyten und Promyelozyten bis auf 38 % belief.

Knochenmark- und Blutuntersuchungen habe ich in zusammen 16 Fällen ausgeführt, von denen 10 akute und 6 chronische Osteomyelitiden betrafen. Die Sternalpunktion ist im akuten Stadium 8mal und im chronischen Stadium 7mal gemacht worden. Theoretisch betrachtet, könnte die Ausführung der Sternalpunktion zumal bei der akuten Osteomyelitis einigermassen gefährlich sein: die Punktion ist ein auf das Knochenmark gerichtetes Trauma; hierbei könnte ein Locus minoris resistentiae entstehen und der Patient könnte eine Osteomyelitis des Sternums bekommen, die sonst eine grosse Seltenheit (Kuperman 1940), aber wegen der durch sie erzeugten Komplikationen (Pleuritis und Mediastinitis) eine relativ gefährliche Lokalisation der Osteomyelitis ist. Deswegen habe ich nicht Serienuntersuchungen ausgeführt und die Sternalpunktion nur in einem Fall (Fall 6) zweimal während des akuten Stadiums gemacht. Komplikationen sind keinmal vorgekommen, aber wegen der erwähnten theoretischen Möglichkeit konnte ich in

dem schwersten und dem einzigen tödlich verlaufenen Fall (Fall 8) keine Sternalpunktion ausführen. Bei den Differenzierungen sind 400 Leukozyten analysiert und die übrigen kernhaltigen Zellen auf diese Menge berechnet worden.

Anschliessend gebe ich die kurzen Epikrisen meiner Fälle wieder [1].

Fall 1. 16 jähr. ♂. Im Krankenhaus 3.XI.42—30.XII.43. Diagnose: *Osteomyelitis acuta tibiae l. a. et femoris dx.* Erkrankte eine Woche, ehe er ins Krankenhaus kam. Temp. 39.6, Allgemeinzustand schlecht, schwere pyogene Allgemeininfektion. Osteomyelitis anfangs in beiden Tibien lokalisiert, 2 Mon. später auch im rechten femur ein Herd. Die Heilung erfolgte langsam, und die Eiterung war sehr reichlich (Staphylokokkeninfektion), das Fieber dauerte etwa 4 Monate. Sternalpunktion gleich bei der Aufnahme und später im chronischen Stadium etwa ein Jahr nach der Erkrankung.

Fall 2. 11 jähr. ♂. Im Krankenhaus 5.V.—8.VIII.43. Diagnose: *Osteomyelitis acuta femoris sin.* Erkrankte 5 Tage, ehe er ins Krankenhaus kam. Temp. 39.7, aber guter Allgemeinzustand, keine schweren Allgemeinsymptome. Das Fieber dauerte etwa einen Monat. Sternalpunktion 31.V.43 ein Monat nach der Erkrankung.

Fall 3. 16 jähr. ♂. Im Krankenhaus 11.VIII.—21.VIII.41. Diagnose: *Osteomyelitis acuta tibiae sin.* Erkrankte 5 Tage, bevor er ins Krankenhaus kam. Temp. 37.5. Allgemeinzustand gut (Staphylokokkeninfektion). Das Fieber sank 11 Tage nach der Erkrankung. Sternalpunktion 11.VIII.41.

Fall 4. 36 jähr. ♂. Im Krankenhaus 27.VIII.—3.IX. 41. Diagnose: *Osteomyelitis acuta fibulae sin.* Erkrankte eine Woche früher. Temp. 37.2, Allgemeinzustand gut (Staphylokokkeninfektion). Sternalpunktion 27. VIII.41.

Fall 5. 5 jähr. ♀. Im Krankenhaus 4. II. 43—12.I.44. Diagnose: *Osteomyelitis acuta tibiae sin.* 10 Tage früher erkrankt. Temp. 38.5, Allgemeinzustand schlecht. In der Blutkultur wachsen Staphylokokken. Die Heilung setzte relativ rasch ein, das Fieber fiel 5 Wochen nach der Erkrankung ab. Sternalpunktion 5.II.43.

Fall 6. 17 jähr. ♂. Im Krankenhaus 12. VII.—13.X.43. Diagnose: *Osteomyelitis acuta femoris dx.* Zwei Tage vorher erkrankt. Temp. 39.9, Allgemeinzustand gut, keine schwere pyogene Allgemeininfektion. Das Fieber sank etwa drei Wochen nach der Erkrankung. Bekam gleich zu Anfang eine kräftige Sulfathiazolbehandlung. Sternalpunktion 15.VII. und 10.VIII.43.

Fall 7. 24 jähr. ♂. Im Krankenhaus 28.I.—15.II.43. Diagnose: *Osteomyelitis acuta costae VI l. dx.* 8 Tage zuvor erst Angina und hierauf Schmer-

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[1] Diese Fälle sind in meiner Arbeit *Über die hämatogene Osteomyelitis* (Duodecim 1944, Suppl. IV) genauer dargestellt.

zen und Schwellung auf der rechten Seite der Thoraxwand. Temp. 38.5, Allgemeinzustand *gut. In der Blutkultur wachsen Influenzabazillen. Die* Heilung erfolgte rasch, das Fieber fiel 6 Tage nach der Operation ab. Es handelte sich offenbar um eine Influenzaosteomyelitis. Sternalpunktion 29.I.43.

Fall 8. 15jähr. ♀. Im Krankenhaus 18.II.—11. III.43. Diagnose: *Osteomyelitis acuta femoris sin. Acc. Pneumonia. Sepsis.* War eine Woche früher erkrankt. Temp. 39.9, Allgemeinzustand schlecht, schwer krank (Staphylokokkeninfektion). Die Kranke starb 3 Wochen nach der Krankenhausaufnahme unter den Symptomen einer schweren pyogenen Allgemeininfektion.

Fall 9. 2jähr. ♂. Im Krankenhaus 31.XII.42.—22.VI.43. Diagnose: *Osteomyelitis acuta humeri sin.* 3 Wochen früher erkrankt und im Kommunalkrankenhauses mehrfach inzidiert. Temp. 38.8, Allgemeinzustand ziemlich schlecht. Das Fieber fiel über einen Monat später ab und der Allgemeinzustand blieb danach gut.

Fall 10. 11jähr. ♂. Im Krankenhaus 27.IX.40.—15.VI.41. Diagnose: *Osteomyelitis acuta femoris dx.* 7 Tage früher erkrankt. Temp. 39.1, Allgemeinzustand verhältnismässig gut (Staphylokokkeninfektion). Das Fieber dauerte über 2 Monate. Sternalpunktion im chronischen Stadium 1.III.41.

Fall 11. 25jähr. ♂. Im Krankenhaus 4.III.—18.III.41. Diagnose: *Osteomyelitis chronica humeri sin.* Vor 5 Jahren akute Osteomyelitis am linken Oberarm. Jetzt seit 2 Monaten an derselben Stelle Schmerzen und Schwellung. Temp. 37.2, Allgemeinzustand gut. Sternalpunktion 5.III.41.

Fall 12. 22jähr. ♂. Im Krankenhaus 2.VII.—25.X.43. Diagnose: *Osteomyelitis chronica femoris dx. (Schizophrenia).* Im Frühling 1942 eine chronisch einsetzende Osteomyelitis am rechten Femur. Temp. 37.6, Allgemeinzustand gut. Sternalpunktion 18.IX.43.

Fall 13. 18jähr. ♂. Im Krankenhaus 22.I.—27.II.43. Diagnose: *Osteomyelitis chronica humeri dx.* Als 7jähriger akute Osteomyelitis im linken Femur, Fistel seit 1937 geschlossen. Zwei Jahre lang zeitweise Schmerzen im rechten Oberarm, die sich jetzt verschlimmert haben, und zu denen sich eine Schwellung gesellt hat. Allgemeinzustand gut, Temp. 37.2.

Fall 14. 48jähr. ♂. Im Krankenhaus 10.VIII.42.—25.X.43. Diagnose: *Osteomyelitis chronica tibiae dx. post fract. sclopetar.* 9.VIII.42 Schussfraktur der rechten Tibia, zu der sich einige Tage später eine Infektion mit sehr reichlicher und langwieriger Eiterung gesellte. Die Wunde verheilte 14 Monate nach dem Trauma. Allgemeinzustand gut. Sternalpunktion 16.VII.43.

Fall 15. 26jähr. ♂. Im Krankenhaus 4.III.—23.IV.41. Diagnose: *Osteomyelitis chronica ulnae sin.* 1929 akute Osteomyelitis, die im rechten Femur, in der linken Tibia und der linken Ulna lokalisiert war. Am linken Unterarm hat die ganze Zeit eine Fistel bestanden. Temp. 37.3, Allgemeinzustand gut. Sternalpunktion 5. III.41.

Fall 16. 28jähr. ♂. Im Krankenhaus 27.XII.40—17.VII.42. Diagnose: *Osteomyelitis chronica femoris sin.* Von klein auf zeitweise Schmerzen im linken Oberschenkel. Seit September 1940 heftige Schmerzen. Im Dezember 1940 wurden röntgenologische Knochenveränderungen festgestellt. Temp. 37.4, Allgemeinzustand gut. Später stieg die Temperatur und der Allgemeinzustand begann sich zu verschlechtern. Eiterung sehr reichlich und Heilungstendenz schlecht. Alles in allem 11mal operiert (3mal Sequestrotomie und 8mal Inzision). Wird als unheilbar in ein anderes Krankenhaus verlegt. Sternalpunktion 20.III.41.

Der Charakter der akuten Fälle wechselt hochgradig. Fall 1 und 8 waren schwere septische Osteomyelitiden. Fall 5 war ebenfalls schwer, aber die Heilung vollzog sich relativ rasch, ebenso Fall 10. Als schwere akute Osteomyelitis kann auch Fall 9 gelten, der aber nicht gleich bei Beginn der Krankheit in Behandlung gekommen ist, sodass man die Blutbilder erst 3 Wochen nach der Erkrankung verfolgen konnte. Die übrigen Fälle waren relativ leicht, und in Fall 4 verursachte die Krankheit nicht einmal einen Temperaturanstieg. Von den chronischen Osteomyelitiden waren die Fälle 11, 12, 13 und 15 Osteomyelitisrezidive, Fall 16 eine sehr schwere primär chronisch einsetzende Osteomyelitis und Fall 14 eine aus einer Schussfraktur hervorgegangene Ostitis, die ich deswegen einbegriffen habe, weil dabei eine sehr schwere und langwierige Eiterung auftrat.

Die Sternalpunktion ist in den akuten Fällen 1—7 ausgeführt worden, und die Ergebnisse sind in Tab. 1 dargestellt [1].

Die in den Sternalpunktaten vorkommenden Veränderungen schwanken hochgradig, und es stellt sich heraus, dass sie in grossen Zügen von der Schwere des Falles abhängen. Das Verhältnis der Erythroblasten zu den Leukozyten beträgt durchschnittlich 1:14, was offenbar von der starken Vermehrung der myeloischen Zellen herrührt. In Fall 4, der sehr leicht war, war das erwähnte Verhältnis 1:7, also annähernd normal, in Fall 1 wiederum 1:19, ebenso in Fall 5.

Die Menge der *eosinophilen* Zellen ist in den akuten Fällen ungefähr normal (durchschnittlich 4 %), und es ist zu beachten, dass in Fall 5, der relativ schwer und bei dem die Reaktion des Knochenmarks ziemlich stark war, im Anhang der Krankheit 7 % Eosinophile auftraten, desgleichen in Fall 6, der nicht so schwer war, aber

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[1] In den Tabellen sind bei den Prozentsätzen der Zellen Dezimalen angewandt worden, obgleich die Genauigkeit der Untersuchungsmethode dies nicht voraussetzt.

mit hohem Fieber begann. Die Anzahl der *Myeloblasten* ist unverändert. Sie schwankt zwischen 1 und 2 % bei einem Mittelwert von 1.5 %. Dagegen gewahrt man in einigen Fällen eine starke Reaktion hinsichtlich der *Myelozyten* und *Promyelozyten*. In Fall 1 und 5 hat die Zahl der Promyelozyten deutlich die normalen Werte überschritten, ebenso die Zahl der Myelozyten in Fall 1. In Fall 5 machen diese Zellen insgesamt 28 % und in Fall 1 volle 42 % aus, sodass hierin nach Nordenson und Klima eine sehr starke Reaktion zum Ausdruck kommt. Die Zahl der *Metamyelozyten* hält sich im allgemeinen innerhalb normaler Grenzen, aber die Menge der *stabkernigen Leukozyten* ist im allgemeinen und zumal in den leichteren Fällen erhöht. Sie schwankt zwischen 18 und 40 %. Die *segmentkernigen Leukozyten* sind in den meisten Fällen vermindert, in Fall 1 machen sie nur 4 % aus.

Die Zahl der *Lymphozyten* ist niedriger als normal und schwankt zwischen 8 und 19 %. Die *Retikulum- und Plasmazellen* sind vermehrt, aber nicht in grossem Umfang. Nur in Fall 1 kommen ihrer 34 (je 400 Leukozyten berechnet) vor, aber in den anderen Fällen ist keine nennenswerte Vermehrung wahrzunehmen. Die Mitosen sind nicht zahlreicher als gewöhnlich. Insbesondere in den schwereren Fällen erscheinen pathologische Veränderungen, wie Plasmavakuolen und grobe Granulation in den Zellen.

Die Sternalpunktate der chronischen Osteomyelitiden sind in Tab. 2 dargestellt.

Das Verhältnis der Erythroblasten zu den Leukozyten ist ungefähr dasselbe wie in den akuten Fällen, nämlich 1: 12, und schwankt zwischen 1: 9 und 1: 17, sodass auch hier eine myeloische Hyperplasie vorliegt. Charakteristisch für die chronischen Osteomyelitiden scheint die Vermehrung der stabkernigen Leukozyten zu sein. Ihre Menge variiert zwischen 19 und 39 % und beträgt durchschnittlich 29 %. Die allerdeutlichste myelozytär-promyelozytäre Reaktion kommt in Fall 14 vor, wo die Totalsumme dieser Zellen 29 % ausmacht. Es ist zu beachten, dass in Fall 16, der seitens seines Krankheitsbildes schwer war, bei dem vor Ausführung der Sternalpunktion etwa anderthalb Monate lang Fieber bestanden hatte und die Eiterung sehr reichlich war, wobei sich ein grosser Sequester im Femur abstiess, die Myelozyten und Promyelozyten zusammen nur 20 % ausmachen und im Knochenmark vorwiegend eine stabkernige Reaktion auftritt, in dem die Zahl der Lympho-

Tabelle 1.

Die Sternalpunktate der akuten Osteomyelitis-Fälle.

Nr.	Datum		Zahl auf 400 L							%									
		Weisse Mitosen	Rote Mitosen	Proerythrobl.	Makrobl.	Normobl.	Megakar.	Retikulum & Plasmaz.	Monoz.	Lymphoz.	Neutr. segm. Leukoz.	Neutr. stabk. Leukoz.	Neutr. Metamyeloz.	Neutr. Myeloz.	Neutr. Promyeloz.	Myelobl.	Eos. Myeloz. & Leukoz.	Bas. Myeloz. & Leukoz.
1	4/11.42	2	0	0	7	15	0	34	1.25	11.5	4.0	20.0	16.25	27.0	14.75	2.0	3.25	0
2	31/5.43	0	1	1	8	32	0	15	0	8.5	19.25	32.0	18.0	12.5	6.0	1.25	2.5	0
3	11/8.41	0	1	4	7	34	0	8	1.0	8.5	12.75	39.75	14.25	12.0	8.0	1.75	2.0	0
4	28/8.41	0	0	2	5	46	0	5	0.25	8.25	11.25	37.0	24.5	11.5	4.25	1.0	1.25	0.75
5	5/2.43	1	0	1	2	18	0	6	0	15.75	12.25	21.25	14.5	15.75	12.25	0.75	7.25	0.25
6	15/7.43	1	0	2	5	20	0	9	0	18.75	8.0	17.75	22.75	15.0	8.25	2.25	7.25	0
	10/8.43	0	0	4	4	13	0	9	0	6.75	23.0	28.0	14.5	16.0	6.75	0.75	4.25	0
7	29/1.43	0	1	4	7	31	0	16	1.5	13.5	30.75	22.25	13.5	7.25	6.25	2.25	2.5	0.25

Tabelle 2.

Die Sternalpunktate der chronischen Osteomyelitis-Fälle.

Nr.	Datum	%										Zahl auf 400 L						
		Bas. Myeloz. & Leukoz.	Eos. Myeloz. & Leukoz.	Myelobl.	Neutr. Promyeloz.	Neutr. Myeloz.	Neutr. Metamyeloz.	Neutr. stabk. Leukoz.	Neutr. segm. Leukoz.	Lymphoz.	Monoz.	Retikulum- & Plasmaz.	Megakar.	Normobl.	Makrobl.	Proerythrobl.	Rote Mitosen	Weisse Mitosen
1	10/8.43	0.25	6.75	1.25	7.25	15.5	17.5	25.25	7.25	18.5	0	13	0	29	1	3	2	4
10	1/3.41	0.25	3.25	0.75	9.5	14.5	17.75	27.0	21.25	5.25	0.5	9	0	29	4	2	0	0
11	5/3.41	0.25	2.25	1.5	11.25	13.0	15.75	39.0	7.5	9.0	0.5	14	1	24	7	2	2	2
12	18/9.43	0.25	4.5	1.25	8.25	13.75	11.25	29.75	10.25	20.75	0	13	0	22	3	2	0	1
14	16/7.43	0.25	2.5	1.0	10.25	19.0	19.5	21.0	14.0	9.5	0	10	0	30	11	2	2	2
15	5/3.41.	0	2.75	0.75	6.25	16.75	11.0	19.0	29.0	14.5	0	12	1	22	2	0	0	1
16	20/3.41	0.5	3.75	0.5	8.0	12.0	19.25	37.25	13.5	5.25	0	8	0	23	10	2	0	1

zyten auf 5 % sinkt. In Fall 11, bei dem es sich um das akute Stadium einer chronischen Osteomyelitis handelte, beläuft sich die Menge der Stabkernigen auf 39 % und diejenige der Promyelozyten auf 11 %. Eine bei den chronischen Osteomyelitiden vorkommende auffallendere Abweichung z. B. von den Normalwerten Virkkunens ist die relativ grosse Zahl der Stabkernigen und die Verminderung der Segmentkernigen; auch Promyelozyten kommen etwas mehr als normalerweise vor. Die Eosinophilen betragen 2—7 %, und Lymphozyten sind auch in den chronischen Fällen etwas weniger als in der Norm vorhanden, durchschnittlich 12 %.

Es hat also den Anschein, als ob die Schwere des Krankheitsbildes bei den chronischen Osteomyelitiden viel weniger auf die Reaktion des Knochenmarks einwirkt als bei den akuten. Trotzdem die Fälle ihrem Charakter nach ziemlich hochgradig verschieden sind — ich möchte besonders die schlechte Heilungstendenz und den relativ schlechten Allgemeinzustand des Patienten in Fall 16 hervorheben — wechseln die Veränderungen in den Sternalpunktaten nicht erheblich. Dies beruht offenbar darauf, dass das Knochenmark bei der akuten Reizung vollkommen anders als bei der chronischen reagiert.

Die Blutbilder meiner akuten Osteomyelitisfälle sind in Tab. 3 dargestellt. Hieraus ersieht man einige charakteristische Veränderungen.

In mehreren Fällen erscheint im Anfang der Krankheit eine starke Leukozytose, die allmählich verschwindet. Die Zahl der Leukozyten bei Beginn der Krankheit schwankt zwischen 6,900 und 34,400. Die niedrigste Leukozytenmenge kommt in Fall 8 vor, der schwer war und tödlich ausging; vor dem Tode stieg die Zahl der Leukozyten auf 12,800. Dies stimmt mit der alten Beobachtung überein, dass eine niedrige Leukozytenmenge im Anfang der Krankheit bei einer schweren Infektion ein schlechtes Zeichen ist. Bei der Pneumonie wurde dies schon von Rieder (1892) konstatiert, und dasselbe erweist die Statistik Forssells (1942) über die im städtischen Maria-Krankenhauses zu Helsinki behandelten Pneumonien. Bei der akuten Osteomyelitis scheint jedoch die Leukozytenzahl bei Beginn der Krankheit durchaus nicht immer in einem bestimmten Verhältnis zur Schwere der Krankheit zu stehen. In Fall 5, der relativ schwer war, beliefen sich die Leukozyten bei der Aufnahme auf 10,900 eine Woche später stieg ihre

Zahl auf 15,600. In Fall 3, der leicht war, aber bei dem an der Tibia ein grosser subperiostaler Abszess entstand, betrugen sie 10,500. In Fall 1, wo es sich um eine schwere multiple Osteomyelitis handelte und der Allgemeinzustand des Patienten lange Zeit schlecht blieb, wurden anfangs 16,200 Leukozyten gezählt, aber ihre Menge sank bald und blieb dann die ganze Zeit relativ niedrig. Die grösste Leukozytenmenge, 34,400. trat in Fall 10 auf, der relativ schwer war, und in dem leichten Fall 7 betrug ihre Zahl 24,100. –

Aus den oben beschriebenen Fällen darf man wohl schliessen, dass man aus der Leukozytenzahl an sich im Anfangsstadium der akuten Osteomyelitis keine sicheren Schlussfolgerungen ziehen kann. Eine stabilere Beurteilungsgrundlage erhält man erst, wenn man das Blutbild mit dem klinischen Krankheitsbild vergleicht. Wenn die Leukozytenzahl in einem klinisch schweren Fall niedrig ist, ist dies vom Standpunkt der Prognose der Krankheit ein schlechtes Zeichen, aber man muss hierbei die fortlaufenden Veränderungen verfolgen und kann erst einen dauernd niedrigen Leukozytenzahl als ernstes Symptom betrachten. Es ist natürlich, dass die normale Reaktion des Organismus bei einer schweren akuten Osteomyelitis mit reichlicher Eiterung in einer Leukozytose zum Ausdruck, kommt, und dass die Verminderung der Leukozyten parallel mit dem Abklingen der klinischen Symptome erfolgt. Die Ausnahmen von dieser Regel erweisen, dass der Krankheitsverlauf ungewöhnlich ist und geben Veranlassung. den Zustand des Patienten genau zu verfolgen.

Die Linksverschiebung des neutrophilen Blutbildes folgt der Leukozytenzahl nicht. Am allerstärksten tritt sie in Fall 1 auf, wo die Stabkernigen bei Beginn der Krankheit 63 % ausmachen und ausserdem 11 % Metamyelozyten und 3 % Myelozyten vorhanden sind. Die Zahl der Leukozyten sinkt schon nach Verlauf einer Woche auf annähernd normale Werte und bleibt danach ziemlich niedrig, aber die starke Linksverschiebung dauert sehr lange, sodass die Stabkernigen 3 Monate nach der Erkrankung noch 25 % und die Metamyelozyten 3 % ausmachen, und noch 5 Monate nach der Erkrankung liegt eine erhebliche Linksverschiebung vor. Die Heilung in dieser Fall vollzog sich sehr langsam, und der Allgemeinzustand des Patienten blieb lange Zeit schlecht. In Fall 3 und 4, die leicht waren, kommt keine Linksverschiebung

Tabelle 3.

Die Blutbilder der akuten Osteomyelitis-Fälle.

Nr.	Datum	Hb (Sahli)	Erythroz.	Index	Leukoz.	Neutroph.	Myeloz.	Metamyeloz.	Stabkern.	Segmentkern.	Basoph.	Eosinoph.	Monoz.	Lymphoz.	SR
1	4/11. 42	79	4280	0.83	16200	87.0	3.0	11.0	63.0	10.0	0	0	3.0	10.0	89
	11/11. 42	37	2100	0.88	10100	80.0	1.0	4.0	57.0	18.0	0	0	2.0	18.0	139
	20/11. 42	40	2660	0.76	8100	77.0	0	5.0	48.0	24.0	0	0	1.0	22.0	150
	2/12. 42	39	2410	0.81	7000	62.0	0	5.0	23.0	34.0	0	0	3.0	35.0	135
	9/12. 42	39	2450	0.81	8300	66.0	0	3.0	27.0	36.0	0	0	6.0	28.0	140
	17/12. 42	39	2410	0.81	5400	64.0	0	2.0	24.0	38.0	0	1.0	4.0	31.0	
	23/12. 42	40	2480	0.83	7100	63.0	0	3.0	24.0	36.0	0	3.0	3.0	31.0	139
	30/12. 42	43	2510	0.86	8600	69.0	0	5.0	24.0	40.0	0	0	1.0	30.0	139
	7/1. 43	46	2810	0.82	9200	65.0	0	2.0	23.0	40.0	0	0	2.0	33.0	143
	15/1. 43	33	2120	0.78	5700	65.0	0	2.0	30.0	33.0	0	0	1.0	34.0	137
	21/1. 43	35	2180	0.83	7900	65.0	0	2.0	28.0	35.0	0	0	4.0	31.0	127
	27/1. 43	38	2230	0.86	6000	70.0	0	2.0	25.0	43.0	0	3.0	4.0	23.0	139
	3/2. 43	38	2300	0.82	8100	71.0	0	3.0	25.0	43.0	0	0	1.0	28.0	132
	11/2. 43	42	2520	0.84	6500	49.0	0	2.0	24.0	23.0	0	1.0	1.0	50.	134
	18/2. 43	42	2580	0.84	6800	63.0	0	1.0	19.0	43.0	0	0	5.0	32.0	123
	25/2. 43	45	2820	0.80	5800	62.0	0	0	17.0	45.0	0	0	4.0	34.0	105
	5/3. 43	50	3180	0.80	7700	52.0	0	2.0	20.0	30.0	0	0	2.0	46.0	9.4
	11/3. 43	54	3280	0.84	9100	60.0	0	0	18.0	42.0	0	2.0	2.0	36.0	124
	18/3. 43	57	3210	0.82	10100	57.0	0	0	27.0	30.0	0	5.0	.50	33.0	

	Datum														
	1/4. 43	48	3040	0.80	10900	72.0	0	0	47.0	25.0	0	1.0	3.0	24.0	122
	10/4. 43	49	3100	0.79	6300	50.0	0	0	27.0	23.0	0	2.0	2.0	46.0	124
	17/4. 43	49	2776	0.88	8500	49.0	0	0	11.0	38.0	0	2.0	13.0	36.0	
	22/4. 43	49	3512	0.70	7700	44.0	0	0	14.0	30.0	0	12.0	8.0	36.0	
	29/4. 43	50	3280	0.78	7500	59.0	0	0	10.0	49.0	0	6.0	2.0	39.0	120
2	31/5. 43	47	2920	0.81	8800	64.0	0	0	5.0	59.0	1.0	1.0	5.0	29.0	46
	7/6. 43	49	2980	0.84	7900	58.0	0	0	3.0	55.0	1.0	1.0	0.	40.0	86
	15/6. 43	50	2900	0.86	6600	45.0	0	0	2.0	43.0	2.0	3.0	5.0	45.0	107
	23/6. 43	55	3000	0.90	6400	55.0	0	0	2.0	53.0	1.0	3.0	0	41.0	82
	1/7. 43	58	3280	0.90	6800	45.0	0	0	3.0	42.0	0	2.0	5.0	48.0	94
	20/7. 43	69	4040	0.86	7000	58.0	0	0	6.0	52.0	1.0	2.0	2.0	37.0	72
3	11/8. 41	86	4680	0.94	10500	78.0	0	0	8.0	70.0	0	0	10.5	11.5	57
	14/8. 41	85	4520	0.94	10400	74.0	0	0	7.0	67.0	0	2.0	12.5	11.5	90
4	28/8. 41	75	4380	0.85	8200	59.0	0	0	0	59.0	0.5	0.5	7.0	33.0	60
5	5/2. 43	63	3310	0.95	10900	68.0	0	0	22.0	46.0	1.0	0	3.0	28.0	60
	12/2. 43	51	2770	0.94	15600	78.0	0	0	20.0	58.0	0	1.0	1.0	20.0	90
	19/2. 43	55	2940	0.95	6600	69.0	0	0	13.0	56.0	1.0	1.0	1.0	28.0	113
	27/2. 43	55	3160	0.89	6000	50.0	0	0	5.0	45.0	1.0	6.0	4.0	39.0	130
	6/3. 43	55	3320	0.83	10500	71.0	0	0	6.0	65.0	1.0	1.0	4.0	24.0	
	13/3. 43	51	3080	0.85	9500	63.0	0	0	6.0	57.0	1.0	4.0	2.0	30.0	116
	20/3. 43	55	3210	0.86	9000	67.0	0	0	3.0	64.0	1.0	5.0	3.0	24.0	
	27/3. 43	54	3210	0.84	9200	64.0	0	0	4.0	60.0	0	5.5	2.0	28.5	70
	5/4. 43	48	2960	0.83	9050	69.0	0	0	5.0	64.0	0	0	0	31.0	112
	19/4. 43	54	3560	0.77	7500	68.0	0	0	1.0	67.0	1.0	1.0	2.5	27.0	82
	3/5. 43	55	3610	0.76	8300	60.0	0	0	2.5	57.5	0	2.5	3.5	34.0	59
	17/5. 43	55	3610	0.76	8900	73.0	0	0	6.0	67.0	0.5	2.0	4.0	20.5	65
	31/5. 43	56	3720	0.76	9500	63.5	0	0	6.0	57.5	0	3.0	4.5	29.0	63
	7/6. 43	61	3850	0.80	7800	64.5	0	0	1.5	63.0	1.5	1.0	7.0	26.0	75

Tabelle 3. (Forts.).
Die Blutbilder der akuten Osteomyelitis-Fälle.

Nr.	Datum	Hb (Sahli)	Erythroz.	Index	Leukoz.	Neutroph.	Myeloz.	Metamyeloz.	Stabkern.	Segmentkern.	Basoph.	Eosinoph.	Monoz.	Lymphoz.	SR
5	21/6. 43	59	3450	0.87	7900	63.5	0	0	1.0	62.5	1.5	3.0	5.0	27.0	62
	5/7. 43	63	3800	0.83	10100	58.0	0	0	7.0	51.0	1.0	0	6.0	36.0	62
	20/7. 43	55	3690	0.76	9200	59.5	0	0	1.5	58.0	1.5	5.0	3.5	31.0	60
	2/8. 43	57	3900	0.73	9900	65.5	0	0	3.0	62.5	0.5	1.5	2.0	30.0	73
	16/8. 43	59	3620	0.82	9400	58.0	0	0	2.5	55.5	0.5	3.5	9.0	29.0	65
	30/8. 43	61	3790	0.82	9600	64.0	0	0	4.0	60.0	0.5	4.0	8.0	23.5	78
	13/9. 43	61	3820	0.80	7400	63.5	0	0	2.5	61.0	1.5	2.0	2.0	31.0	75
6	15/7. 43	73	3900	0.93	13000	77.0	0	0	19.0	58.0	0	1.0	4.0	18.0	38
	21/7. 43	70	3860	0.92	9600	72.0	0	0	21.0	51.0	0	1.0	2.0	25.0	109
	28/7. 43	70	3780	0.94	9900	77.0	0	0	11.0	66.0	0	0	2.0	21.0	102
	5/8. 43	70	3700	0.94	7800	68.0	0	0	8.0	60.0	0	0	1.0	31.0	105
	11/8. 43	68	3680	0.94	7500	68.0	0	0	3.0	65.0	3.0	1.0	3.0	25.0	103
	21/8. 43	65	3500	0.92	11000	65.0	0	0	4.0	61.0	1.0	2.0	2.0	30.0	110
	2/9. 43	64	3500	0.90	11100	62.0	0	0	2.0	60.0	0	3.0	5.0	30.0	110
	1/10. 43	70	3900	0.89	7200	68.0	0	0	4.0	64.0	0	3.0	0	29.0	89
7	29/1. 43	81	4480	0.92	24100	87.0	0	0	13.0	74.0	0	0	2.0	11.0	63
	5/2. 43	67	3850	0.88	7000	68.0	0	0	13.0	55.0	1.0	1.0	2.0	28.0	83
	12/2. 43	77	4440	0.88	11100	69.0	0	0	13.0	56.0	1.0	1.0	2.0	27.0	30

Gr.	Datum														
8	20/2.43	75	4704	0.92	6900	80.0	0.5	4.5	34.5	40.5	0	0.5	4.5	15.0	30
	2/3.43	46	2472	0.93	12800	87.0	0.5	1.5	12.0	73.0	0.5	1.0	2.5	8.0	30
	8/3.43	40				89.5	2.5	3.0	15.5	68.5	0	1.0	1.5	8.0	20
9	4/1.43	48	2720	0.89	32800	66.5	0	0.5	9.5	56.5	0	0	9.0	24.5	144
	12/1.43	53	3060	0.88	15100	56.0	0	0.5	9.0	46.5	0.5	1.0	8.0	34.5	91
	19/1.43	49	2980	0.84	13900	69.5	0	0	2.5	67.0	1.5	3.0	4.5	21.5	117
	27/1.43	49	2970	0.84	16600	66.5	0	0	6.5	60.0	0	0	5.5	28.0	95
	2/2.43	47	2940	0.81	22200	70.0	0	0	5.0	65.5	0.5	1.0	7.0	21.5	126
	9/2.43	50	3260	0.78	13400	61.0	0	0	5.0	56.0	0.5	3.0	6.0	29.5	130
	15/2.43	51	3360	0.77	11700	60.5	0	0	2.0	58.5	0	3.5	5.5	30.0	96
	23/2.43	54	3640	0.75	11800	50.0	0	0	4.0	46.0	0	2.5	10.0	37.5	68
	2/3.43	52	3580	0.74	7000	46.5	0	0	1.5	45.0	0	1.0	7.5	45.5	77
	8/3.43	52	3780	0.70	12000	47.5	0	0	1.0	46.5	0.5	2.0	7.5	43.0	92
	15/3.43	57	4040	0.71	10100	51.5	0	0	0	51.5	1.0	0.5	4.5	13.0	36
	22/3.43	58	4180	0.71	14600	49.5	0	0	3.0	46.5	1.5	1.5	7.5	40.5	82
	29/3.43	57	4140	0.70	9100	37.0	0	0	1.0	38.0	0.5	3.5	7.5	48.5	31
	20/4.43	61	4420	0.69	13400	56.5	0	0	2.5	51.0	0.5	0.5	6.5	36.0	
10	2/10.40	65			31900										
	3/10.40				31100										
	4/10.40				27600										
	5/10.40	60			21200										
	7/10.40				17400										
	9/10.40				11600										
	11/10.40				11000										
	15/10.40				1210										
	18/10.40				1000										
	21/10.40				11100										
	25/10.40	69	3390	0.91	9800	43.0	0	0	9.0	31.0	0	1.0	7.0	49.0	56

Tabelle 4. Die Blutbilder der chronischen Osteomyelitis-Fälle.

Nr.	Datum	Hb (Sahli)	Erythroz.	Index	Leukoz.	Neutroph;	Metamyeloz.	Stabkern.	Segmentkern.	Basoph.	Eosinoph.	Monoz.	Lymphoz.	SR
1	27/7.43	55	3300	0.83	6400	41.0	0	4.0	37.0	0	5.0	2.0	52.0	98
	11/8.43	60	3510	0.85	6000	22.0	0	5.0	17.0	0	13.0	4.0	60.0	73
	2/9.43	63	3710	0.85	7100	53.0	0	6.0	47.0	0	9.0	6.0	32.0	75
	14/10.43	70	4230	0.82	7200	53.0	0	4.0	49.0	0	5.0	7.0	35.0	78
11	5/3.41	66	3950	0.85	10800	68.0	0	2.0	66.0	1.0	1.0	8.0	22.0	95
12	22/9.43	80	4420	0.90	7300	41.0	0	4.0	37.0	0	4.0	2.0	53.0	40
	29/9.43	80	4490	0.90	7600	44.0	0	4.0	40.0	1.0	4.0	3.0	48.0	7
	13/10.43	81	4220	0.97	5100	47.0	0	5.0	42.0	0	4.0	9.0	40.0	8
13	25/1.43	65	4010	0.81	16300	81.0	0	11.0	70.0	0	0	3.0	16.0	66
	27/1.43	61	3870	0.80	12300	68.0	0	8.0	60.0	0	1.0	3.0	28.0	55
	9/2.43	65	3860	0.86	8500	59.0	0	2.0	57.0	1.0	3.0	3.0	34.0	20
	16/2.43	72	4210	0.86	6500	71.0	0	2.0	69.0	0	4.0	1.0	24.0	
	22/2.43	74	4280	0.88	7400									
14	16/7.43	75	4320	0.86	12400	69.0	0	10.0	59.0	0	0	2.0	29.0	22
	21/7.43	76	4300	0.88	10400	41.0	0	6.0	35.0	0	1.0	2.0	56.0	20
	28/7.43	75	4380	0.87	8600	53.0	0	4.0	49.0	0	1.0	3.0	43.0	34
	21/8.43	78	4400	0.88	8800	49.0	0	4.0	45.0	1.0	2.0	3.0	45.0	20
15	5/3.41	84	4690	0.91	10400	59.0	0	2.0	57.0	0	2.0	11.0	28.0	55
16	28/12.40	67	3760	0.91	9200	74.0	0	6.0	68.0	0	2.0	4.0	20.0	120
	27/1.41	62	3670	0.86	9400									108
	11/2.41	62			8600									110
	17/3.41	57	3520	0.81	8600	72.0	0	8.0	64.0	2.0	2.0	6.0	18.0	122
	1/4.41	57	3560	0.81	8800									146
	22/4.41	51	3240	0.80	15000	77.0	2.0	17.0	58.0	0	0	6.0	17.0	120
	23/5.41	57	3120	0.84	8100	60.0	0	7.0	53.0	0	1.0	6.0	33.0	

vor, aber in Fall 5 ist sie ziemlich stark: Stabkernige 22 %.
Metamyelozyten unt Myelozyten treten indessen nicht auf, und 3
Wochen später ist die Linksverschiebung verschwunden. In Fall
7 sind die Veränderungen des Blutbildes geringer, aber in Fall 8,
der zum Exitus führte, gross: Stabkernige anfangs 34.5 %, Myelo-
zyten 0.5 % und Metamyelozyten 4.5 % sowie später, kurz vor dem
Tode, Stabkernige 15.5 %, Myelozyten 2.5 % und Metamyelozyten
3 %. In Fall 9 ist die Linksverschiebung trotz der starken Leuko-
zytose geringer. Blutbilder liegen jedoch nicht gleich von Beginn der
Krankheit sondern erst von 3 Wochen nach der Erkrankung vor.

Nach der Meinung Payrs ist die Linksverschiebung des neu-
trophilen Blutbildes bei der akuten Osteomyelites ein schlechtes
Zeichen, insbesondere dann, wenn die Leukozytenzahl gleich-
zeitig nicht entsprechend hoch ist. Aus den oben beschriebenen
Fällen ersieht man, dass dies zutrifft; man kann sogar sagen, dass
*die Linksverschiebung ein symptom ist, dass regelmässiger als die
Leukozytose auftritt.* Eine starke Linksverschiebung, zumal wenn
sie nicht rasch vorübergehend ist, kann man wohl als zeichen dafür
betrachten, dass es sich um einen schweren Fall handelt.

Die Zahl der Eosinophilen ist bei akuten Infektionen im allge-
meinen herabgesetzt (Schulten), aber es gibt auch Ausnahmen von
dieser Regel. H. Lenhartz konstatierte bei septischen Endokardi-
tiden mit völlig infauster Prognose bisweilen eine normale oder
nur wenig herabgesetzte Eosinophilenzahl. Die Vermehrung
der Eosinophilen in einem späteren Stadium der Krankheit ist
ein gutes Zeichen (Schulten, Harkins). In allen meinen akuten
Fällen war die Zahl der eosinophilen Zellen im Anfang der Krank-
heit niedrig, zwischen 0 und 1 %. In den Fällen 1, 3, 5, 7 und 9
fehlten sie im Blute vollständig. In meinem schwersten septischen
Fall (Fall 8) kommen jedoch bei Beginn der Krankheit 0.5 % und
später 1 % davon vor. Im allgemeinen vermehren sich die Eosino-
philen in diesen Fällen rasch, abgesehen von Fall 1, wo sie noch
5 Wochen nach der Erkrankung vollkommen fehlen und erst nach
der 18. Woche, wo das sehr schwere Krankheitsbild sich zu bessern
anfängt, regelmässig im Blut vorkommen.

Die Monozytenmenge wechselt nicht regelmässig. Im Anfang der
Krankheit werden sie in meinen akuten Fällen zu 2—10.5 % ange-
troffen, und in dem späteren Stadium kann man keinen regelmäs-
sigen Anstieg in ihrer Menge bemerken. Dasselbe lässt sich von den

Lymphozyten sagen, deren Menge bei Beginn der Krankheit zwischen 10 und 33 % variiert. In Fall 8 sinkt ihre Menge (auch die absolute) jedoch, ebenso die Monozytenzahl, was an seinem Teil auf die schlechte Prognose der Krankheit hinweist.

In Fall 1 und 5 hatte man Gelegenheit, die Blutbilder von Anfang der Krankheit an regelmässig zu verfolgen. In dem ersteren Fall handelte es sich um eine schwere septische multiple Osteomyelitis, bei dem die Genesung lange Zeit recht fraglich war, bei dem letzteren um eine septische Tibiaosteomyelitis, die auch schwer war, aber bei der die Heilung rascher folgte. Aus Tab. 3 ersehen wir, dass zumal in Fall 1 zeitweise eine leichte Leukozytose auftritt. Diese Anstiege der Leukozytenzahl fallen mit den gelegentlichen Verschlimmerungen der Krankheit zusammen. Gleichzeitig vermehren sich die Stabkernigen, und mit Rücksicht auf die absoluten Mengen scheint die Linksverschiebung eine empfindlichere Reaktion als die Leukozytose zu sein. Die Monozytenzahl weist keinen sicheren regelmässigen Anstieg auf; in Fall 1 steigt die Lymphozytenmenge ein wenig. Schillings monozytäre Abwehrphase tritt also hierin nicht in Erscheinung, ebensowenig in diesem Stadium die lymphozytäre Heilphase.

Das Hämoglobin und die Erythrozytenzahl sinken, wie zu erwarten, nur in den schweren Fällen. In Fall 1 sinkt das Hämoglobin während der ersten Behandlungswoche von 79 % auf 37 % und die Erythrozytenzahl von 3,280,000 auf 2,100,000. In Fall 5 ist der Abfall viel geringer, aber in Fall 8 ist er steil, von 75 % auf 46 %. Bei den schweren akuten Osteomyelitiden stellt sich also, wie überhaupt bei der pyogenen Allgemeininfektion rasch eine hypochrome Anämie ein, deren Stärke eine gute Grundlage für die Beurteilung der Schwere der Krankheit bildet.

Die Senkungsreaktion der roten Blutkörperchen erweist, dass die Senkungsgeschwindigkeit, insbesondere in schweren Fällen hochgradig gesteigert ist. Die grössten Werte kommen jedoch nicht gleich im Anfang der Krankheit sondern etwas später vor. Gleich bei der Aufnahme schwankt SR in meinen akuten Fällen zwischen 30 und 89 mm (die Bestimmungen sind nach Westergren ausgeführt worden, wobei lediglich der Senkungswert der ersten Stunde berücksichtigt wurde), aber schon nach Verlauf einer Woche steigt die Senkungsgeschwindigkeit erheblich und im allgemeinen über 100 mm an. Die Senkungsreaktion ist nicht so empfindlich wie die

Veränderungen des Blutbildes, die früher eintreten (Reichel). Ihr diagnostischer Wert ist bei chirurgischen Krankheiten in der Regel gering, worauf z. B. Hellström und Varga hingewiesen haben, aber bei der Beurteilung des Krankheitsverlauf, der Komplikationen und eventuell der Prognose kann ihr doch eine wichtigere Bedeutung zukommen. In den vorliegenden Fällen bemerkt man, dass SR lange Zeit hoch bleibt. Obwohl das Blutbild in grossen Zügen normal wird, kommen Werte über 100 mm vor; z. B. in Fall 6, der nach einem akuten und hochfieberhaften Beginn rasch abklingt und nur eine leichte Lokalisation im Femur aufweist, ist die Senkungsreaktion noch nach 6 Wochen nach der Erkrankung 110 mm. Im diagnostischen Sinne hat man bei der akuten Osteomyelitis keinen Nutzen davon, denn bei den Weichteilphlegmonen bemerkte ich ebenso hohe Werte. Desgleichen hängen ihre Schwankungen während der Krankheit später nicht so regelmässig wie die Schwankungen des Blutbildes vom Krankheitsverlauf ab, sondern scheinen ganz unbestimmt in ihrem Auftreten.

Die Blutbilder meiner chronischen Osteomyelitisfälle sind in Tab. 4 dargestellt. Hierin kommen keine grösseren Veränderungen vor. In Fall 1 bleibt die Leukozytenzahl während des chronischen Stadiums (beinahe ein Jahr nach der Erkrankung) normal und schwankt zwischen 6,000 und 7,200. Die Linksverschiebung ist verschwunden, indem die Menge der Stabkernigen zwischen 4 und 6 % variiert, und Eosinophile kommen mehr als gewöhnlich vor (5—13 %). Die Lymphozytenmenge ist auch gestiegen; ihre Grenzwerte in den chronischen Fällen lauten 32 und 60 %, und der Monozytengehalt wechselt zwischen 2 und 7 %. Die Senkungsreaktion weist ebenso hohe Werte auf, aber bei den im akuten Stadium befindlichen Fällen sinkt sie nach der Operation und Heilung rasch. Eine Leukozytose tritt in den chronischen Fällen im allgemeinen nicht auf; nur in Fall 13 ist die Zahl der Leukozyten anfangs vermehrt (16,300). Eine Linksverschiebung wird nur in Fall 16 in dem schwersten Stadium der Krankheit angetroffen, wo die Stabkernigen 17 % und die Metamyelozyten 2 % ausmachen.

Beim Vergleich der Sternalpunktate und Blutbilder miteinander bemerkt man, dass die Linksverschiebung im Blutbild und eine starke Reaktion im Knochenmark einander im allgemeinen entsprechen, während die Leukozytose un die Veränderungen des Sternalpunktats nicht so regelmässig parallel sind, eine Beobach-

tung, die überhaupt bei akuten Infektionen gemacht worden ist (Klima). Eosinophile Zellen kommen in allen meinen akuten Fällen ungefähr in normaler Menge im Sternalpunktat vor, obgleich sie aus dem Blut in den meisten Fällen vollkommen verschwunden sind. Auch in dem schweren septischen Fall 1, wo Eosinophile zum ersten Mal erst 5 Wochen später und auch dann nur vorübergehend erscheinen, machen sie im Sternalpunktat 3 % aus. In diesen Fällen lässt sich also keine parallele Verminderung der eosinophilen Zellen im Sternalpunktat und im Blut nachweisen, wie sie u. a. von Klima, Rohr, Forssell und Virkkunen nachgewiesen wurde.

Zusammenfassung.

Die durch die Osteomyelitis bedingten Veränderungen des Sternalpunktates sind folgende: Bei schweren akuten Osteomyelitiden kommt eine starke promyelozytäre Reaktion vor. In leichteren Fällen sind die Veränderungen geringfügiger, und es treten relativ viele Stabkernige auf. Bei der chronischen Osteomyelitis ist die Reaktion des Knochenmarks vorwiegend eine Stabkernige. Die Schwere des Krankheitsbildes scheint bei der chronischen Osteomyelitis viel weniger auf die Reaktion des Knochenmarks einzuwirken als bei der akuten. Der Umstand, dass bei der Osteomyelitis ein Teil des funktionierenden Knochenmarks zerstört wird, scheint nicht auf die allgemeine Reaktion des Knochenmarks einzuwirken, und zwar nicht einmal bei der multipeln Osteomyelitis, sondern die Veränderungen des Knochenmarks entsprechen auch hierbei in grossen Zügen den bei akuten Infektionen anzutreffenden Veränderungen.

Die wichtigsten der im Blutbild auftretenden Veränderungen sind die Leukozytose, die Linksverschiebung des neutrophilen Blutbildes und die Eosinopenie. Die Leukozytenzahl schwankt bei der akuten Osteomyelitis hochgradig, und man kann daraus an sich keine Schlussfolgerungen hinsichtlich der Beschaffenheit der Krankheit ziehen, sondern sie muss mit dem klinischen Krankheitsbild verglichen werden. Als normale Reaktion hat bei der akuten Osteomyelitis eine hohe Leukozytenzahl bei Beginn der Krankheit zu gelten. Beim Abklingen der klinischen Symptome sinkt ihre Zahl allmählich. Eine niedrige und zumal eine dauernd nied-

rige Leukozytenzahl ist bei der klinisch schweren akuten Osteomyelitis ein schlechtes Zeichen. Die Linksverschiebung des neutrophilen Blutbildes folgt der Schwere der Krankheit viel regelmässiger als die Leukozytose, und eine starke Linksverschiebung ist als prognostisch schlechtes Zeichen anzusehen. Die Eosinopenie erscheint in allen meinen akuten Fällen. Bei den chronischen Osteomyelitiden sind die Veränderungen des Blutbildes geringfügig.

Die Senkungsreaktion zeigt, dass die Senkungsgeschwindigkeit der Erythrozyten bei den akuten Osteomyelitiden hochgradig steigt. Dieser Umstand erscheint später als die Veränderungen des Blutbildes, erhält sich aber noch lange, nachdem die Krankheit klinisch auszuheilen begonnen hat.

Zwischen der Leukozytose und der Veränderungen des Sternalpunktats ist kein Parallelität wahrzunehmen, während in den akuten Fällen eine deutliche Parallelität zwischen der Linksverschiebung und den Veränderungen des Sternalpunktats nachzuweisen ist. Eine gleichzeitige Verminderung der Eosinophilen im Sternalpunktat und im Blut ist in meinen Fällen nicht vorgekommen. Es ist jedoch zu beachten, dass wiederholte Sternalpunktionen nicht ausgeführt werden konnten.

Weder von den im Sternalpunktat noch von den im Blutbild vorkommenden Veränderungen hat man beim Diagnostizieren der akuten Osteomyelitis Nutzen, weil ähnliche Veränderungen ganz allgemein bei eitrigen Infektionen auftreten. Bei der Prognosenstellung der Krankheit und bei der Verfolgung ihres Verlaufes dagegen kann man wichtige Schlussfolgerungen daraus ziehen. Hierbei muss man sich wohl auf die Verfolgung des Blutbildes beschränken, weil wiederholte Sternalpunktionen im Interesse des Kranken bei der akuten Osteomyelitis nicht in Frage kommen dürften.

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610

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